5 COST-EFFECTIVENESS ANALYSIS (CEA) AND EXPLORING FOR ALTERNATIVE APPROACHES

One of the first questions raised when I started with the health economic analysis of vaccines for developing countries using CEA, is how a decision maker can work with that result if the investment in health care in the country is low, the disease burden therefore large, while the cost-effectiveness threshold recommended by the WHO -that is the GDP per capita-, is much too high.

Under such circumstances everything done to reduce the disease burden must be very cost-effective at quite a high price for that country. Published data about cost-effectiveness results of rotavirus vaccination in Latin-America activated my first suspicion that there is something bizarre with the numbers presented [25]. The analysis showed that one could ask a higher price for the vaccine in low income countries and still be cost-effective compared with the price for low middle income countries. The point was that the authors didn't report any paradox in the analysis presented in table format. I first analysed the same data in a graph to better understand the underlying difference between the numbers by different country type. In a next step I explored how the graphs were constructed given the cost and the effect elements that were in the analysis. One of the options was to reinvestigate the problem more in depth by making the comparison between different country types across the whole world and not only Latin America with a same vaccine using a same CEA technique. The difference by country type remained at the level of the GDP per capita. I wanted to calculate the price range the vaccine will obtain for still remaining cost-effective in countries with different GDP levels. I presented that exercise in the next paper [26].

An important finding of that analysis is that the CEA in countries that have already maturely invested in health care programs will have a CE-price range for a new intervention that appears reasonable. Extra -payment that can be obtained for the extra-health gain achieved is within an acceptable price band. But this approach is completely out of scope for low-income countries because the investment in health care is too low and the need much too high. Here, other techniques than CEA should be used to define health care priorities linked to an economic assessment that identifies priority setting, health goals to be achieved within a reasonable time and budget frame.

One of the techniques I proposed to work with is using optimisation modelling. I first explored the approach for the better positioning of the Human Papilloma Virus (*HPV)* vaccine versus different screening frequency methods and no intervention at all. A very reasonable price level could be identified for emerging and high income markets such as Brazil and the UK [27]. The analysis is quite spectacular for the rich countries as for a same annual budget spent on cervical cancer prevention today but switching the screening frequency to a lower rate while spending the money saved into vaccination, the model predicts an overall benefit in reducing cervical cancer cases up to 45% per year.

But the technique of optimisation modelling can be applied under many different conditions and formats. I investigated the problem of a 2 versus 3 dose vaccination scheme under a fixed budget for rotavirus disease, [28]. Health authorities in many countries work with fixed annual budgets for their prevention programs in health care. They are sometimes exposed to new deals suggested by international bodies about changing the dosing frequency of vaccination programs. It has been suggested that for *Rotarix*® to be used in developing countries it may improve the reduction in diarrhoea events by changing the frequency from 2 to 3 doses. When operating under a fixed budget it doesn't appear obvious to go for a 3 dose scheme when the recommended dosing scheme is 2. Only under extreme circumstances or a perfect combination of 3 factors (low vaccine coverage rate, high cost difference per dose, and high efficacy increase for the third dose), can the 3 dose program result in a better deal.

In the same area of discovering new economic assessment tools for health care I was able to work closely with Dr Mark Connolly from the University of Groningen in the Netherlands from 2008 onwards. We were both looking for new ways of economic evaluation in health care that helps demonstrating where the benefit of a health gain obtained through new interventions is an added value for society instead of focussing on the individual benefit only. The approach should be especially useful for prevention activities such as vaccination. For instance if countries are suffering from a high child mortality rate because of an infectious disease such rotavirus that is a major cause of infant diarrhoea, what could be the incentive for an authority to go for that vaccination? We have the tendency to look very closely to our own silo program of mortality reduction and the Ministry of Health being the main sponsor for such an intervention for obvious reasons. But we thought that there could be additional benefit elsewhere than just having the child mortality reduced if we introduce the vaccine. If that additional benefit is identified elsewhere than there must be a sponsor elsewhere as well.

With Dr Connolly, based on his past experience of exploring new economic approaches in the world of assisted reproduction, we developed what could be seen as an interesting approach for convincing local authorities and not only health authorities to invest in vaccination. The investment can be seen as a method to increase tax payment for the government as a mid to long term benefit if more children survive. The tax flow over time can be huge compared with the small investment one has to do once with vaccination of a child at birth. We fully explored that approach in one publication with Egyptian data that we were able to present to the local health administration [29]. Unfortunately the recent events that occurred in Egypt didn't give us the full chance to move forward with the project, but the initial responses we received from the health administration of that country at that time were extremely encouraging. They finally found a study with results using a language that other decision makers in their governmental organisation could understand: rate of return, net present value, among other terms that is normally used by the finance administration. This program on return on investment for vaccines received much attention from the WHO that sponsored a few other projects in low income countries in Vietnam and Ghana [30].

COMPARING COST-EFFECTIVENESS RESULTS FOR THE SAME INTERVENTION ACROSS DIFFERENT COUNTRIES WORLDWIDE: WHAT CAN WE LEARN?

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Baudouin Standaert[1]
Olivier Ethgen[2]
Rachel Emerson[3]
Maarten Postma[4]
Josephine Mauskopf[5]

[1]GlaxoSmithKline Vaccines, Wavre, Belgium;
[2]Université de Liège, Liège, Belgium);
[3]Emerson Consulting, Tervuren, Belgium;
[4]University of Groningen, Groningen, The Netherlands;
[5]RTI Health International, Research Triangle Park, North Carolina, USA

ABSTRACT

Background: Cost-effectiveness analysis (CEA) using country-specific thresholds tied to gross domestic product (GDP) might not be appropriate in countries with low healthcare investment and a high disease burden as a consequence.

Methods: Using data from previously published CEA of rotavirus vaccination across nine countries worldwide, we calculated the cost-neutral price (P_n) for the new intervention that reflects the price resulting in no net increase in health care costs compared with the current situation, and the maximum price (P_m) obtained with an incremental cost-effectiveness ratio (ICER) at the threshold value of 1 x GDP/capita.

Results: In countries with low GDP/capita the paradoxical finding for rotavirus vaccination is that the P_m is much higher than in countries with a high GDP/capita. On the other hand, the P_n for the low GDP/capita countries is much lower than for high GDP/capita countries because of the low investment in health care.

Conclusions: In countries with low healthcare investment and a high disease burden the difference between the P_n and P_m for rotavirus vaccine which is the price range within which the ICER is below the WHO threshold value, is large. One reason could be that the WHO threshold value may not properly account for the local opportunity cost of health care expenditures. Therefore either alternative threshold values should be selected or alternative economic assessment tools should be considered such as budget optimisation or return on investment if we want to communicate about real economic value of new vaccines in those countries.

INTRODUCTION

Current economic assessment of a new medical intervention such as a drug, device, or vaccine aims to provide local decision-makers with information on the additional benefit generated for the additional cost incurred, compared with the existing situation (1;2). This is most commonly conducted using cost-effectiveness analysis (CEA), with results expressed with incremental cost-effectiveness ratios (ICERs). The ICER can be used to help define an acceptable "value-based" price range for the new intervention, with the maximum acceptable price being the price at which the ICER crosses a defined threshold (2). The Gross Domestic Product (GDP) per capita is a well-accepted threshold measure, as proposed and recommended by the World Health Organization (WHO) (3) (4). If the price of the new technology leads to an ICER below the threshold, that price is qualified as being highly cost-effective following the interpretation of the WHO-guidelines (5).

CEA is a well-established economic assessment technique in healthcare (6) ; (7), (8). It was initially developed in industrialised countries with mature healthcare systems which had already made considerable investments in healthcare infrastructure. More recently, the use of CEA has been extended to economic evaluations of health interventions in developing countries. For example, CEA results for rotavirus vaccination have been reviewed in developed countries (9) and developing countries (10). These two reviews reported that the vaccine was very cost-effective in low-income countries, but the picture was mixed in high-income countries. A similar result was reported by Rheingans *et al.* (2009) comparing the cost-effectiveness and price setting of rotavirus vaccination for different country groups in Latin America from low income (L), via low middle (LM), to upper middle income (UM) (11). They reported that the price per vaccine dose that is cost-effective was higher in L countries than in LM and UM countries. This is counter-intuitive, as it would be expected that the maximum price for favourable cost-effectiveness would be lower in L countries, reflecting the lower income and lower resources available for healthcare, compared with higher-income countries. The authors of these papers did not attempt to explain this paradoxical finding. The analysis provided here builds on these previous reports by seeking to explore how these apparently paradoxical results could arise.

This paper focuses on rotavirus vaccination as an example. It is an interesting example, as the rotavirus vaccine has been the subject of CEA in a range of countries worldwide, and the benefits obtained from the vaccine appear quite different in high- versus low-income countries (12). In low-income countries, the benefit of vaccination is primarily a reduction in the high mortality rate. In high-income countries, in addition to a reduced need for hospital care the benefits are more subtle, such as better time management for working parents (11) (13).

In this paper, first a theoretical framework and interpretation of the "value-based" price range is presented for a new vaccine program. In the next step, an application in practice for rotavirus vaccination using published country-specific data for rotavirus to estimate the "value-based" price range in nine countries was conducted. This allowed an analysis of the relationship of the "value-based" price range for each country and the GDP/capita. Finally, the findings are interpreted and recommendations made for alternative/additional economic evaluations.

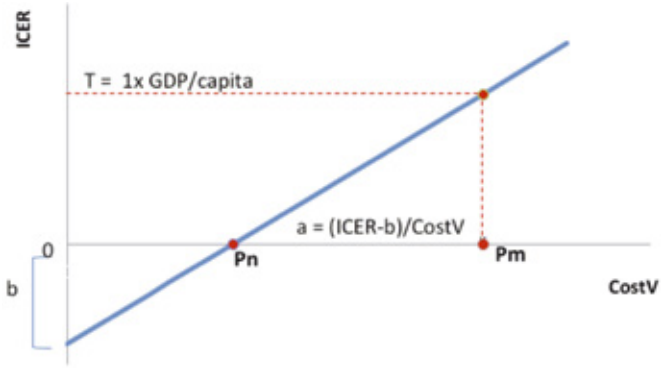
METHODS

Theoretical Framework

The first step demonstrates, using mathematical equations, the relationship between the price of a new intervention, the ICER, the threshold value for cost-effectiveness and the cost-neutral price (Pn) and the maximum price (Pm) linked to that threshold.

The relationship between the ICER and the price of a new intervention is expressed as a linear function ($y = ax + b$), where y (= ICER) is the dependent variable and x (= price or cost of the new intervention) is the independent variable, here the cost

Figure 1 Cost-neutral (Pn) and maximum price (Pm) of the vaccine per dose at a threshold T (for example $40,000/life-year gained)



a, slope; b, intercept; CostV, vaccine cost; Pm, maximum price; Pn, cost-neutral price; ICER, incremental cost-effectiveness ratio; T, Threshold.

of the vaccine (CostV). This relationship is now considered within the context of a static cohort model for modelling the cost-effectiveness of the intervention of the rotavirus vaccine (14). Additional equations and variables help to specify which exact parameters define the slope of the line (a) and which the intercept (b) that is the remaining disease cost after the impact of the new intervention divided by the difference in disease outcomes attributable to the new intervention. Calculating the association between the price of the new intervention and the ICER allows testing the price range over which it is still cost-effective. This is defined here as the price range for which the ICER lies below the threshold value, defined as 1 x GDP per capita (3). The linear function also indicates at what price the ICER equals zero (because of no difference in total cost with the intervention compared with the total cost without the intervention). This is referred to as the cost-neutral price (Pn). The maximum price (Pm) above which a new product is no longer cost-effective is defined by the point where the threshold value intersects with the increasing linear function for new interventions that are more effective but result in higher total costs than with the current health care program (see Figure 1).

Now, we further elaborate on the mathematical properties of the relationship described above. In its simplest form, the relationship between the ICER and the cost (price) of a new intervention (vaccine) is defined by the following equations:

$$\frac{(CostD_V + CostV) - CostD_{NV}}{E_{NV} - E_V} = ICER <= T$$

$$\frac{CostV}{E_{NV} - E_V} + \frac{(CostD_V - CostD_{NV})}{E_{NV} - E_V} = ICER$$

$$a = \frac{1}{(E_{NV} - E_V)}$$

$$b = \frac{(CostD_V - CostD_{NV})}{(E_{NV} - E_V)}$$

where:

- $CostD_V$: remaining disease-related cost with vaccination
- CostV: acquisition cost of the new intervention (vaccine)
- $CostD_{NV}$: initial disease-related cost in the absence of vaccination (no vaccine)
- E_V: remaining health losses (effects) with vaccination
- E_{NV}: health losses without vaccination (no vaccine)
- ICER: incremental cost-effectiveness ratio
- a: slope of the line
- b: intercept
- T= Threshold (here defined as the Gross Domestic Product (GDP)/capita

From the equations above, the slope (a) is defined by the inverse of the effect difference, while the intercept (b) is defined by the cost difference without including CostV divided by the effect difference.

There is one additional variable to be defined in the equations, the vaccine impact on disease-related costs and negative health outcomes:

$$CostD_V = CostD_{NV} * (1 - VaccineEffect_C)$$

$$E_V = E_{NV} * (1 - VaccineEffect_E)$$

where:

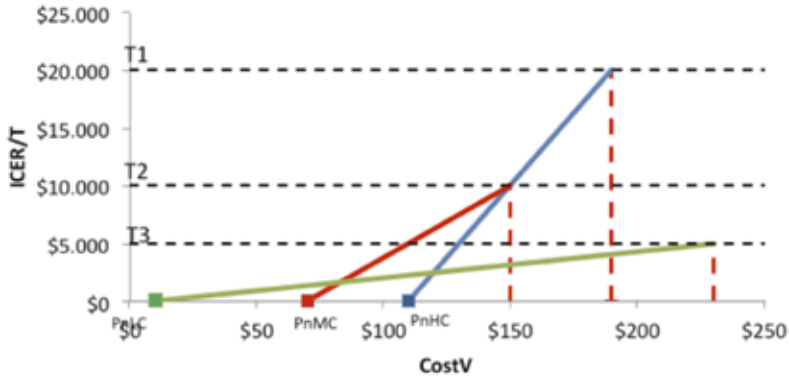
- $VaccineEffect_C$ and $VaccineEffect_E$: the vaccine effects on costs and negative outcomes (range of values between 0 and 1) obtained from randomised clinical trials entered into the model. For simplicity only two factors are assessed here, disease-specific mortality (negative outcomes) and hospitalisation (costs). The output of E_V and E_{NV} is expressed in survival loss expressed in life-years, in which the difference between the two is presented as a gain in survival time.

The vaccine may have different effects on costs and health outcomes in different elements of the disease burden. For example, the effect of the vaccine in reducing hospitalisations, medical visits or total numbers of cases may vary, and the effect on the total cost will depend on the frequency of each of these elements in the total cost burden. To simplify the model, in the present paper only one cost component is considered, hospitalisation. In rotavirus disease, it is normally assumed that deaths occur in hospitalised cases. Thus, in this simplified case that reflects an environment with a well-established health care system, the effects of the vaccine on costs (hospitalisations) and health outcomes (deaths) are likely to be equi-proportionate. It may be different in those situations where the health care system is less well developed.

Hypothetical baseline model

To illustrate this theoretical framework a model was constructed for a hypothetical developed country with a threshold value of $40,000/life-year gained, equivalent to the GDP per capita of the hypothetical country. The currency was selected as

Figure 2 Cost-neutral (Pn) and maximum price (Pm) at different thresholds and slope lines. The green line indicates a country with a low threshold (T3), the red line a country with an intermediate threshold (T2), and the blue line a country with a high threshold (T1). As the threshold increases the cost-neutral point (where the line intercepts the X-axis) shifts to the right and the slope steepens, reflecting higher healthcare expenditure and lower remaining disease burden



CostV, vaccine cost; ICER, incremental cost-effectiveness ratio; $P_{nLC,}$ cost neutral price in Low Income country; $P_{nMC,}$ cost neutral price in Middle income country; $P_{nHC,}$ cost neutral price in High income country; T, Threshold

$ because international data are commonly expressed in $. The model development is based on experience obtained from rotavirus disease and the impact of paediatric rotavirus vaccination in Europe. The model assumes vaccine coverage of 100%, but the coverage rate has no impact on the ICER as long as a static epidemic model is used, because the coverage rate affects both sides of the ratio (higher coverage results in both higher costs and higher effect). Table I summarises the input values selected.

The baseline value for $CostD_{NV}$ was $60/subject, calculated from data in studies in a recent literature review (9). It represents the average cost for rotavirus hospitalisation in Europe per child in the birth cohort (i.e. the total cost of rotavirus hospitalisations averaged across all children in the cohort). As only a small percentage of children in the birth cohort will be hospitalised for rotavirus, the cost per subject is much smaller than the cost per hospitalised case or per hospitalisation event. The baseline value for E_{NV} (0.00031/subject) is based on the following reasoning. The maximum individual loss in health outcome is the loss of full life expectancy at birth (78 years, discounted at 3% per year = 31 years). That value is multiplied by the disease-specific mortality rate (0.00001 per year) for infants in the region to estimate the individual loss in health outcomes per unvaccinated subject in the infant population. The perspective is that of the healthcare system.

Figure 2 shows how the vaccine price range (Pm-Pn) can shift and change for countries with different cost-effectiveness thresholds but also different potential gains in health outcomes resulting in a change of the slope. As the threshold value increases, Pm becomes larger. In addition, as the absolute effect difference becomes smaller because of a smaller disease burden in the absence of vaccination

(E_{NV}) the slope of the line steepens. As the amount of current spend on the disease increases, Pn becomes larger. Such a situation would be expected in a high-income country (indicated by the high GDP per capita threshold value), with a low disease burden (indicated by the steeper slope) and a higher current expenditure on the disease (Pn and Pm both shifted to the right). Thus the slope of the line is likely to be steeper and the absolute difference between Pn and Pm lower for countries with a higher GDP/capita associated with a lower disease burden and higher disease expenditures in the absence of vaccination (see Figure 2).

Country-specific data

The next step is to apply this theoretical approach to real-life published data from nine countries across the world for which the cost-effectiveness of rotavirus vaccine has been evaluated using a similar model (15), taking the country-specific GDP per capita as the threshold value. The model adjusts for different current disease-related costs and different vaccine impacts in high income and low income countries, and for other factors related to country-specific conditions such as life expectancy, unit cost (expressed in $), disease management, and GDP, among others. Effects are consistently discounted at 3% per year. The same current-intervention $CostD_{NV}$ (hospitalisation) and E_{NV} (disease-specific mortality) variables are used as in the base case model. Cost variables were not discounted because of the short period (the first 2 to 3 years) when health care expenditure on vaccination and disease-related cost occurs.

RESULTS

Hypothetical baseline model

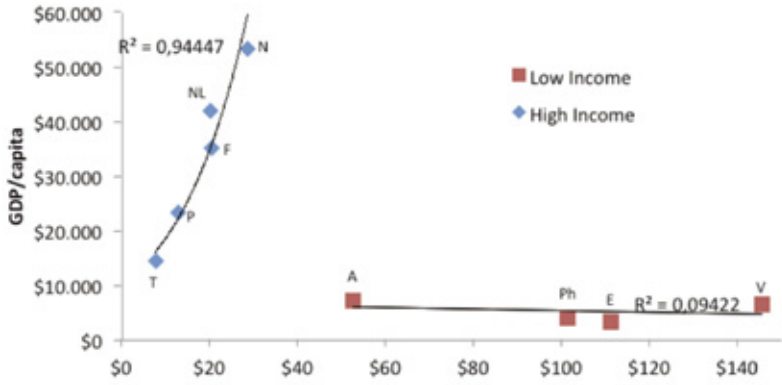
Table I shows the results of the base-case model.

Table 1 Variables, formulae, input values and output results to calculate the ICER, the cost-neutral price (Pn), and the maximum price of a new intervention (Pm) using a hypothetical model

Variable	Formula	Input	Output
$CostD_{NV}$		$60	
$CostD_{v}$	$CostD_{NV}$*(1-VaccineEffect)		$6
CostV at Pn	$CostD_{NV}$–$CostD_{v}$		$54
E_{NV}		0.00031	
E_{V}	E_{NV}*(1-VaccineEffect)		0.000031
ICER (=Y) at Pn	(($CostD_{v}$+CostV)-$CostD_{NV}$)/(E_{NV}-E_{V})		$0
VaccineEffect		0.9	
a	1/(E_{NV}-E_{V})		3584.23
b	($CostD_{v}$-$CostD_{NV}$)/(E_{NV}-E_{V})		-193548.39
Y	a*Pn + b		$0
Threshold Value		$40,000/E	
Maximum price/course (Pm)	(40,000-b)/(a)		$65.16

a: slope of the linear regression; b, intercept; Pm, maximum price; Pn, cost-neutral price; $CostD_{v}$: remaining disease-related cost with vaccination; $CostD_{NV}$: initial disease-related cost in the absence of vaccination (no vaccine); CostV, vaccine cost; E, effect unit (life-year gained); E_{NV}: health losses without vaccination (no vaccine); E_{V}: remaining health losses (effects) with vaccination; ICER, incremental cost-effectiveness ratio;

Figure 3 Relationships between baseline values of Pm and GDP by country



Countries with low GDP per capita (squares): A, Algeria; E, Egypt; Ph, Philippines; V, Vietnam.
Countries with high GDP per capita (diamonds): F, France; N, Norway; NL, Netherlands; P, Portugal; T, Turkey.
Pm, maximum price; GDP, gross domestic product

The two critical points of the vaccine price, Pn and Pm, related to the ICER and the threshold value are shown in Figure 1. The cost-neutral point (Pn=$54) and the maximum price point (Pm=$65.16) define the price range over which the vaccine could still be cost-effective with the threshold set at $40,000 per life-year gained.

Country-specific data

For each country, country-specific values for the variables of current cost ($CostD_{NV}$) and loss in health outcomes (E_{NV}) were used to calculate the Pn and Pm of the vaccine at the country-specific threshold (GDP per capita). This exercise provides a better understanding of the meaning of a cost-effectiveness result for countries with different income levels, expressed through their GDP values. Table II presents the input data for each country, obtained from published sources as follows: Vietnam (16), Egypt (17), Philippines (18), Algeria (19), Turkey (20), Portugal (21), France (15), Netherlands (22), Norway (23). Life expectancy data for all countries were obtained from WHO Health Statistics 2013(24), and GDP per capita from World Bank data (25). Table II also shows the $CostD_{NV}$ and E_{NV} per subject with the calculated Pn and Pm at the GDP threshold for each country.

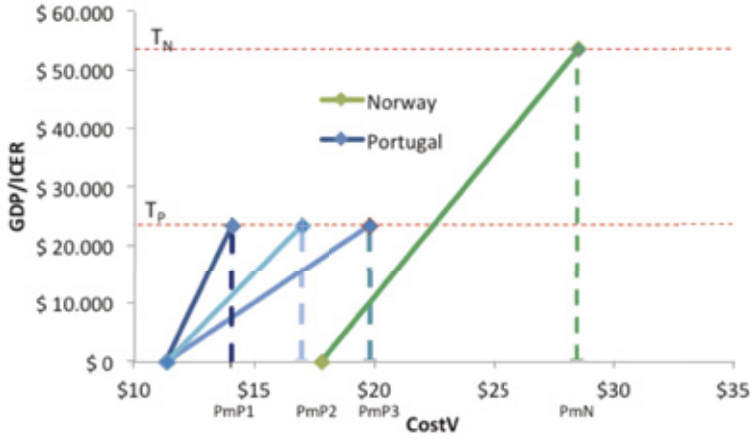
Figure 3 presents the relationship between Pm and GDP per capita across the nine countries, plotted from the data in Table II. It shows that the countries fall into two groups for the relationship between Pm and the country-specific GDP threshold values. For the cluster of countries with a GDP per capita >$10,000, the lower the GDP threshold, the lower the Pm. In this group of countries, the slope is steep, with a fairly narrow range between Pn and Pm (see Table II).

Table 2 Input and output values for each country selected

Country	Vietnam (16)	Egypt (17)	Philippines (18)	Algeria (19)	Turkey (20)	Portugal (21)	France (15)	Netherlands (22)	Norway (23)
Birth cohort	1,639,000	1,909,000	2,266,887	621,790	1,257,583	109,457	750,000	187,910	60,000
Life Expectancy (y) (24)	71.6	68.0	66.6	74.3	73.3	76.6	77.5	78.5	80
Hospitalisations up to age 5 y	32,331	53,342	17,448	11,000	36,797	1,200	17,932	2,940	905
Hospital rate for the birth cohort	1.97%	2.79%	0.77%	1.77%	2.93%	1.10%	2.39%	1.56%	1.51%
Hospital cost per event	$20	$19	$45	$650	$400	$2,172	$1,400	$2,172	$2,382
Deaths up to age 5 y	6,050	3,200	4,438	300	13	1	9	2	1
Death rate	0.37%	0.17%	0.20%	0.048%	0.0010%	0.0009%	0.0012%	0.0011%	0.0017%
GDP (25)	$3,359	$6,455	$4,080	$7,325	$14,393	$23,363	$35,068	$42,023	$53,396
VE in the model	64%	64%	64%	64%	87%	90%	90%	90%	90%
Pn (per dose)	$ 0.12	$ 0.15	$ 0.16	3.76	$ 5.58	$ 11.30	$ 15.80	$ 16.09	$ 17.81
Pm (per dose)	$ 111.26	$ 145.61	$ 101.29	$ 52.61	$ 7.61	$ 14.04	$ 20.53	$ 20.13	28.56
Price range (Pm-Pn)	$ 111.14	$ 145.46	$ 101.13	$ 48.85	$ 2.03	$ 2.74	$ 4.73	$ 4.04	$ 10.75
$CostD_{NV}$	$ 0.39	$ 0.54	$ 0.35	$ 12.69	$ 11.70	$ 23.81	$ 33.47	$ 33.98	$ 35.97
$CostD_{V}$	$ 0.14	$ 0.23	$ 0.03	$ 5.18	$ 0.541	$ 1.22	$ 1.87	$ 1.80	$ 0.38
$CostD_{NV}$-$CostD_{v}$	-$ 0.25	-$ 0.31	-$ 0.32	-$ 7.51	-$ 11.16	-$ 22.59	-$ 31.60	-$ 32.18	-$ 35.59
E_{NV}	-0.105	-0.0471	-0.0560	-0.014	-0.000297	-0.00025	-0.000297	-0.00022	-0.00041
E_{V}	-0.039	-0.0021	-0.0064	-0.0006	-0.000014	-0.00002	-0.000027	-0.000023	-0.000004
E_{NV}-E_{V}	0.066	0.045	0.0496	0.0134	0.000283	0.00023	0.000270	0.000197	0.000406
a	15	22	20	75	3534	4348	3704	5076	2463
b	-4	-7	-6	-560	-39431	-98217	-117037	-163350	-87660

GDP, gross domestic product; VE, vaccine efficacy; y, years; a: slope of the linear regression; b, intercept; Pm, maximum price; Pn, cost-neutral price; $CostD_{NV}$: initial disease-related cost in the absence of vaccination (no vaccine); CostDv: remaining disease-related cost with vaccination; E_{NV}: health losses without vaccination (no vaccine); $E_{V:}$ health losses after vaccination

Figure 4 Effect on the maximum price (Pm) of increasing the threshold (GDP in Norway compared with Portugal) and increasing the disease burden (number of rotavirus deaths per year in Portugal increased from P1 to P2 to P3)



T_N =Threshold for Norway; T_P = Threshold for Portugal.
Pm, maximum price; CostV, vaccine cost; GDP, gross domestic product; ICER, incremental cost-effectiveness ratioCountries with high GDP per capita (diamonds): F, France; N, Norway; NL, Netherlands; P, Portugal; T, Turkey.
Pm, maximum price; GDP, gross domestic product

Figure 4 shows an example that illustrates how the Pm will vary according to the cost-effectiveness threshold value with a similar disease burden in the absence of vaccination. The difference between Norway (GDP per capita $53,396) and Portugal (GDP per capita $23,363) illustrates that effect on Pm with a higher threshold. The Pm with one rotavirus death per year is $28.52 in Norway, considerably higher than the maximum price of $14.04 in Portugal (left-hand of the three lines for Portugal in the figure [dash-dotted line]). The three lines for Portugal illustrate the effect of increasing the disease burden in the absence of vaccination from one rotavirus death per year (left-hand [dash-dotted] line) to two rotavirus deaths per year (middle [dashed] line) and then to three rotavirus deaths per year (right-hand [dashed] line) while assuming expenditure for the disease treatment remains constant. It can be seen that as the disease burden (number of rotavirus deaths per year) increases, as expected Pm also increases even without a change in the threshold. This is because as the disease burden at baseline increases with the increasing number of deaths, the benefit of the vaccine in reducing the disease burden will also be higher in absolute value, the slope of the line in Figure 4 will be lower and therefore the price range over which the vaccine is cost-effective will be larger. The vaccine price range for cost-effectiveness (Pm-Pn) is, however, much larger in Norway than in Portugal, despite a disease burden that is 1.3 times lower in Norway than Portugal.

In the second cluster of countries, those with a low GDP per capita, the pattern of systematic decline of the Pm with lower GDP per capita no longer fits the data. The

baseline disease-related healthcare costs are so low ($CostD_{NV}$), and the remaining health burden (E_{NV}) so high, that the slope factor 'a' is also very low (see Table II). The slope factor is given by the equation:

$$a = \frac{1}{(E_{NV} - E_V)}$$

The slope angle is very shallow because of the high reduction in losses in health outcomes, and the Pn value is close to zero because of the low current expenditure per case for the disease and thus the potential for only minimal cost offsets.

DISCUSSION

An important outcome from the analyses presented in this paper is that the results for rotavirus vaccination split the countries into two clusters with different characteristics using the GDP per capita as a measure of distinction.

Countries with a high GDP/capita

CEA has been applied mainly in higher income countries for many years now as a technique currently used to compare the value of alternative treatments and/or in combination with threshold values representing willingness to pay for an incremental unit of health as the basis for "value-based" pricing. It is an established method in health economic assessment to help to define the price at which a new intervention is considered good value for money compared with the current standard of care at the individual, most often, patient level (26) (27).

Typically, a new intervention has an impact on both the cost and the effect side in the ICER. CEA makes most sense in capturing the value of a new intervention when there is investment in healthcare for the disease of interest but with disease burden still remaining. Under such circumstances a new intervention can achieve both an important cost offset and a reasonable effect gain. It is then meaningful to estimate a cost per life-year or quality-adjusted life year gained in relation to a pre-specified threshold within a price range. Such situations are likely to occur within mature healthcare markets. ICER values calculated from CEA can be useful in defining the acceptable price range in such countries. The steeper the line in Figure 1, the narrower the price band over which the ICER moves from Pn to Pm. When Pn equals Pm, the focus of price-setting may shift from cost-effectiveness to cost savings.

The maximum price in this group of countries is strongly influenced by the threshold value (GDP per capita) and the remaining disease burden in the absence of vaccination. As the threshold value increases, the maximum price also increases. In addition, as the disease burden in the absence of vaccination increases, the slope of the line decreases and the maximum price increases even without a change in the threshold, as illustrated in the present analysis using Norway and Portugal as examples.

Countries with low GDP/capita

The situation is quite different when conducting CEA outside mature healthcare markets. This reflects an environment with low existing healthcare investment ($CostD_{NV}$) and high disease burden (E_{NV}) as a consequence. The low existing healthcare expenditure on the disease allows minimal scope for cost offsets, so the Pn is close to zero. The high disease burden has the potential for large reductions in health outcome losses, so an effective intervention can be cost-effective (as defined by the GDP per capita threshold) over a wide price range, because of the low slope.

This wide price range within which rotavirus vaccination is cost-effective offers a possible explanation for the paradoxical results for rotavirus vaccination CEA reported in the literature. Reviews of rotavirus vaccination reported high cost-effectiveness in low-income countries and a mixed picture in high-income countries (10). A study in Latin America found that the vaccine price that was apparently cost-effective was higher in low-income countries than in middle-income countries (11). Yet it is clear that high prices are not affordable or acceptable for low-income countries. The present analysis suggests that the apparently better cost-effectiveness results at a relatively high intervention price in countries with low GDP per capita reflects the large increases in health outcomes possible in such environments.

In situations with high potential increases in health outcomes accompanied by low current health care expenditures, ICER values calculated by conventional CEA have limited value in defining a reasonable price band for a new intervention. Even if the estimated ICER value indicates that a high price would be cost-effective based on a 1x GDP threshold, the price may be rejected on the basis of the affordability of the acquisition cost (28). A price close to the Pn is likely to be preferred by the low-income country, but as the Pn is likely to be very low (because low existing healthcare expenditure offers minimal scope for cost offsets), such a price might not be seen as reasonable by the seller of the new intervention. Thus, if Pn and Pm define price bands in low-income countries that are questionable at the extremes for both payers and producers, CEA performed under these conditions might not be able to serve the same function in low-income countries as in high-income countries, where CEA is used to help define a reasonable price band.

Although the value of $10,000 GDP per capita that differentiates the two groups of countries in this analysis is an arbitrary threshold, it acts as a proxy for the degree of healthcare development in a country. Countries in the group with a high GDP per capita typically have well established healthcare systems with infrastructure already in place. In these countries, the fixed cost of healthcare infrastructure is already accounted for and variable costs for treatment are well accepted. In these cases decisions about new interventions can be made at the margin using incremental costs and benefits for individuals, as described in the ICER calculated by conventional CEA that assumes that prices are a fair representation of opportunity costs. Conversely, in the countries with a low GDP per capita, healthcare infrastructure may be limited and the healthcare system not yet fully developed. Because of this, prices defined as acquisition costs may not reflect the true opportunity cost of the intervention. In these situations,

affordability and practical considerations such as the alternative possible uses for the additional healthcare investment (including other health investments or non-health investments) are important considerations.

Potential future directions

Our results suggest that CEA is not necessarily the optimum economic analysis method for defining a feasible price band for a new intervention in low-income countries (29). Measuring shadow prices could be an alternative if cost-benefit analysis or CEA are used for economic assessment of new interventions in those situations (30). In low-income environments with low health investment and a high disease burden, almost any improvement in health will require extra spending. The question therefore should be phrased not as a comparison of the new intervention with the existing situation which could be considered as a substitution economy, but as a consideration of which alternative interventions would provide the greatest additional health benefit for a given amount of extra money spent –an add-on economy instead of substitution (31).

Health problems that affect a whole population (as is often the case in low-income countries) should be assessed using economic approaches, tools or techniques that describe the problem well at the population level. In addition the impact of increased spending on health care on other sectors of the economy should be included in the analyses.

Budget optimization modelling (BOM) (32) and return on investment (ROI) (17) are possible alternative economic techniques for estimating the true value of a new intervention in low-income countries. The choice of technique should be driven by the economic question asked, a good understanding of the economic problem to be solved, data availability, and the requirements of the decision-makers who need to understand and use the economic analysis.

BOM is attractive when the problem is one of integrating different management options into a specific health goal within certain constraints, such as budgets and/or logistics (33). Its application is not especially complicated. Furthermore, the BOM is well suited to the type of problem that needs to be addressed in low healthcare investment areas. Instead of comparing a new intervention with the existing situation, which as described here has weaknesses when applied to countries with a low GDP/capita, it considers the question of how best to optimise the use of the health investment budget available today. It is essentially a more flexible and dynamic version of budget impact assessment. However, a limitation of budget optimisation is that it is more difficult to evaluate the effects of uncertainty than in conventional CEA, because the effects of varying the proportions of different interventions in the mix have to be taken into account, as well as uncertainty in the parameters describing each intervention.

ROI analysis is also attractive. It is based on the premise that the health problem must be substantial at population level and compares different investment policies in terms of benefit within that population projected over time as a function of tax

payment/income for the government. It can compare investment in prevention through vaccination with either doing nothing or increasing healthcare infrastructure to reach the same health benefit level. However, a limitation is that it considers health benefits only in terms of the effects on future tax revenues, and does not take into account intangible benefits such as the improvement in human welfare arising from reductions in the disease burden.

A further area of uncertainty is whether the average GDP per capita reflects the right threshold value (34). First, the distribution of GDP per capita in low-income countries is often skewed, and much of the population may receive little benefit from any healthcare services offered because they do not have access to them. This issue is not reflected in the average per-capita GDP value, but is reflected in the remaining health problem (E_{NV}). For example, Egypt has a relatively high GDP per capita, close to the value reported for Algeria, while the disease burden (E_{NV}) is high and comparable with populations such as the Philippines (see Tables II). Second, GDP per capita does not necessarily relate to the investment a country is willing to make in healthcare, which may be affected by other competing priorities.

The present analysis has limitations. Not all the different costs and benefits related to rotavirus vaccination have been included in the analysis, as the focus was only on the parameters that drive the main results, hospitalisation and mortality. However, a more detailed assessment is not likely to change the main discrepancy between the clusters of countries with high versus low income. Furthermore, the analysis has only investigated a single intervention and disease, rotavirus vaccination. The next step would be to explore whether other disease areas show similar patterns, which would indicate whether the findings are likely to be generalizable.

In conclusion, the paradoxical results of CEA in countries with low GDP per capita described in this paper, suggest that conventional CEA may have limited applicability for defining an acceptable price range in such situations. This may be because current methods for cost-effectiveness analyses do not properly account for the opportunity costs of the new intervention in low income countries. Alternative economic methods may be better suited to the economic assessment of healthcare interventions in low-income countries, and this should be explored in greater detail.

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EBUDGET CONSTRAINT AND VACCINE DOSING: A MATHEMATICAL MODELLING EXERCISE

Baudouin A Standaert[1], *Desmond Curran*[1*], *Maarten J Postma*[2*]

[1]GlaxoSmithKline Vaccines, Wavre, Belgium
[2]University of Groningen, Groningen, the Netherlands

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ABSTRACT

Background: Increasing the number of vaccine doses may potentially improve overall efficacy. Decision-makers need information about choosing the most efficient dose schedule to maximise the total health gain of a population when operating under a constrained budget. The objective of this study is to identify the most efficient vaccine dosing schedule within a fixed vaccination budget from a healthcare payer perspective.

Methods: An optimisation model is developed in which maximizing the disease reduction is the functional objective and the constraint is the vaccination budget. The model allows variation in vaccination dosing numbers, in cost difference per dose, in vaccine coverage rate, and in vaccine efficacy. We apply the model using the monovalent rotavirus vaccine as an example.

Results: With a fixed budget, a 2-dose schedule for vaccination against rotavirus infection with the monovalent vaccine results in a larger reduction in disease episodes than a 3-dose scheme with the same vaccine under most circumstances. A 3-dose schedule would only be better under certain conditions: a cost reduction of >26% per dose, combined with vaccine efficacy improvement of ≥5% and a target coverage rate of 75%. Substantial interaction is observed between cost reduction per dose, vaccine coverage rate, and increased vaccine efficacy. Sensitivity analysis shows that the conditions required for a 3-dose strategy to be better than a 2-dose strategy may seldom occur when the budget is fixed. The model does not consider vaccine herd effect, precise timing for additional doses, or the effect of natural immunity development.

Conclusions: Under budget constraint, optimisation modelling is a helpful tool for a decision-maker selecting the most efficient vaccination dosing schedule. The low dosing scheme could be the optimal option to consider under the many scenarios tested. The model can be applied under many different circumstances of changing dosing schemes with single or multiple vaccines.

BACKGROUND

The initial dosing schedule of a new vaccine is based on the results obtained in randomised clinical trials which evaluate the efficacy at the individual level. When real-world data on effectiveness become available questions may be raised over whether the initial dosing schedule is the most appropriate one to achieve the maximum benefit at the population level from limited available healthcare resources. This is an interesting economic question in which the number, timing and efficacies of vaccine doses should be assessed in detail. In the analysis

presented here we evaluate the impact of a change in number of vaccine doses and the economic value of such a change under the constraint of a fixed vaccine budget, a situation most likely to occur in low-income countries. We have used the monovalent rotavirus vaccine (*Rotarix*®[a]) as a concrete example as it has recently been suggested that the number of doses for this vaccine should be increased in low-income countries [1].

Rotavirus infection results in a high burden of acute gastroenteritis disease in children, especially in low-income countries, with approximately 450,000 deaths that could be prevented each year by vaccination [2]. There are currently two vaccines available against rotavirus [3], but all analyses here performed are presented with the 2-dose attenuated single human rotavirus strain monovalent rotavirus vaccine (*Rotarix*®) [4;5].

In 2009 the World Health Organization recommended the inclusion of rotavirus vaccination in routine immunization programs worldwide [6]. However, trials and observational studies conducted in low-income countries have reported lower vaccine efficacy than in high-income countries [7-9]. Many hypotheses have been formulated to explain this, but no definitive conclusions have been drawn [10;11]. Nevertheless, the morbidity and mortality impact expected in low-income countries greatly surpasses that in high-income countries, despite the lower inferred vaccine efficacy [12].

To improve the results of vaccination it has been recently suggested that adding one dose to the existing vaccine dosing schedule could improve overall vaccination efficacy [1]. However this is by no means certain as 3- dose vaccine efficacy studies with other rotavirus vaccine products tested in low-resource environments have also reported lower efficacy estimates compared with wealthier settings [13;14]. In low-income countries where healthcare budgets are tight, a 2-dose schedule could be a more efficient option than a 3-dose schedule as fewer administrations may reduce the overall vaccination cost [15]. Administration may be particularly expensive in those countries, as the costs of the logistics required to maintain a cold chain may be high [16;17]. A 2-dose schedule may also achieve improved compliance and completion of the total dosing at an earlier time point as it obviously requires fewer doses to obtain full vaccination compared with a 3-dose schedule [18].

Given the considerations above, administering an additional dose could improve the rotavirus vaccine efficacy, but it raises an economic question of whether this would provide acceptable added value. Traditional health economic analysis would calculate the incremental cost-effectiveness ratio (ICER) to explore whether the additional dose is cost-effective compared with the current 2-dose schedule. If the analysis indicates that the extra budget needed for reaching the extra benefit is acceptable under the local constraints, it then requires that extra budget is found to secure the implementation of this new intervention. However, in low-income countries there may be no extra budget available to administer the additional vaccine dose even if it would be cost-effective. In such environments,

the addition of an extra vaccine dose may be possible only at the expense of cuts elsewhere in the fixed budget. Conversely, it may be possible to improve the clinical results by increasing the vaccine coverage rate without adding an extra dose. Therefore, it may be more appropriate to consider a different economic approach and to compare the clinical outcomes obtained with a 2-dose schedule with a higher vaccine coverage rate versus the clinical outcomes obtained with a 3-dose schedule at a higher vaccine efficacy but a lower coverage rate. In other words, given a fixed budget, when would it be efficient to move to a 3-dose strategy? The solution to this question is no longer driven by a cost-effectiveness threshold but by the fixed budget: what is the best way to spend money under a fixed budget in order to obtain a maximum health benefit? This type of question can best be analysed at the population level (accumulated benefit and cost), in contrast to cost-effectiveness analysis that can be assessed at the individual level. It also seems to be a realistic way for local decision-makers to evaluate the benefit of vaccination strategies [19].

In this paper we evaluate the potential cost and health effect of adding a third dose to the existing 2-dose schedule of the monovalent rotavirus vaccine in low-income countries, using a hypothetical model to explore this. The model uses optimisation theory, in which a wide range of scenarios are explored to find the optimum solution under budget constraint. In sensitivity analysis, we investigate the influence of several variables on the results, including vaccine efficacy, coverage rate, and price per dose.

METHODS

The economic question raised in the introduction, "what is the best way to spend a fixed budget to obtain the maximum health benefit from vaccination?" can best be explored using optimisation or mathematical programming models [20]. The exercise is to reach specific (functional) objectives or goals under certain constraints. In this setting, the objective function is to maximise health benefits. The model has been programmed to evaluate just one particular disease with one intervention type, but different diseases with different interventions assessing a same outcome could be considered as well.

In the particular case of rotavirus disease, the outcome measure, used to assess the benefit, is the total number of diarrhoea events in the population of children aged <5 years, and the objective is to minimise the number of such events. As a direct consequence of this, mortality and hospitalisation rates due to rotavirus disease would also be reduced. We conducted a cross-sectional analysis with an annual budget, estimating events per year in the at-risk population at steady-state. The latter typically reflects the situation when disease spread and vaccine efficacy have reached their equilibrium across the entire at-risk population. The model constraints are:

- Annual vaccination budget is fixed;
- Vaccine efficacy for a 3-dose strategy ≥ than that for a 2-dose strategy;
- Vaccine efficacy for a 3-dose strategy < 150% of that for a 2-dose strategy;

- Cost per dose for a 3-dose strategy < than that for a 2-dose strategy;

The model assumes a fixed cost per dose for the administration and for the logistics to maintain the cold chain. The coverage rate allows a variation between 0% and 100%. No discounting is applied as it concerns a budget analysis.

The model construct is developed in Microsoft *Excel*, using additional Solver tools (Frontline Systems, Inc.) from software specifically designed to be integrated as an add-in into Microsoft *Excel*. The results of the optimisation model indicate which strategy (i.e. a 2- or 3-dose strategy) would produce maximum health benefits under a budget constraint. The analysis is conducted from the perspective of the healthcare payer system. A copy of the model is available as a Microsoft *Excel* spread sheet (see Additional-File-1.xls).

As the current exercise is hypothetical we do not apply it to a specific country. The whole analysis is focussed on the relationships between the critical variables and their relative values.

Sensitivity analysis is conducted by varying three key parameters that affect the results, vaccine efficacy, price, and coverage. The relationships between the variables are as follows: the number of overall diarrhoea events avoided by a 2-dose schedule (y) is a function of the vaccine coverage rate (a), the vaccine efficacy (x) obtained, and the disease population incidence rate (i):

$$y = a * x * i$$

The increment (c) to reach the objective function (maximising the reduction in diarrhoea events) with a 3-dose schedule is a function of the change in the vaccine coverage rate (a_1) and the extra vaccine efficacy (x_1) obtained, compared with a 2-dose schedule, while the population incidence rate remains unchanged:

$$y + c = [(a + a_1) * (x + x_1)] * i$$

The change in coverage rate (a_1) was assumed dependent on the relative price difference per dose between a 2- and a 3-dose vaccine schedule, given a fixed budget for vaccination. There will automatically be a link with the reduction in vaccine coverage rate, if the price difference per dose and per vaccine scheme decreases, as an increase in the vaccine efficacy (x_1) is then required for the 3-dose schedule to keep its advantage over the 2-dose schedule.

Sensitivity analysis should demonstrate what price difference, what vaccine coverage rate, or what vaccine efficacy difference would be required to achieve a change in the preference between the two dosing schedules. In addition, the change in health outcomes will affect the overall management cost of the disease. Changes in vaccine coverage rate and/or vaccine efficacy would be expected to affect the cost drivers for overall disease management costs, such as hospitalisation rate. To address this, we add an evaluation of the budget change for overall disease

management as a relative value to the fixed budget for vaccination as an additional output variable in the sensitivity analysis.

RESULTS

Analysis with fixed data

Tables 1 and 2 provide an example to illustrate the model. Table 1 shows the input data and Table 2 the modelled outputs. This hypothetical example assumed an annual birth cohort of 10,000 children who could be vaccinated. Based on the assessment of disease burden and the financial priorities, the health ministry is assumed to have allocated an annual budget of $200,000 for rotavirus vaccination. The annual incidence rate of rotavirus diarrhoea without vaccination was set at 0.3 per child per year for the at-risk period (from birth up to age 5 years) of the birth cohort, thus an average of 3,000 children per year would be expected to develop diarrhoea without vaccination.

Table 1 Input variables

Parameter	Value
Total vaccination budget	$200,000
Cost/dose for 2-dose vaccine schedule (strategy A)	$13.00
Cost/dose for 3-dose vaccine schedule (strategy B)	$10.00
Diarrhoea incidence rate per child per year	0.30
Vaccine efficacy for 2-dose vaccine schedule (strategy A)	0.60
Vaccine efficacy for 3-dose vaccine schedule (strategy B)	0.65
Number of vaccine doses for strategy A	2
Number of vaccine doses for strategy B	3
Population	10,000
Target vaccine coverage rate	75%
Average treatment cost per diarrhoea event	$50.00

Under strategy A (n_a=2) the cost per dose was set to $13, and thus the cost per course of vaccination was $26 (=$13*2). With a target coverage rate of 75%, the cost of vaccination was estimated at $195,000 (=10,000*0.75*$26) which represents 97.5% of the total available vaccination budget. As such, there would be sufficient budget (i.e. the budget would not be exceeded) and the target coverage rate would be reached. Assuming a vaccine efficacy of 60%, 900 of the 7,500 children in the vaccinated part of the cohort would be expected to develop diarrhoea, in addition to 750 of the 2,500 children in the unvaccinated part of the cohort, yielding a total of 1,650 diarrhoea cases. Thus, the health benefit gained by vaccination with a 2-dose schedule would be a reduction of 1,350 diarrhoea cases (a reduction of 45%) for the full birth cohort, compared with no vaccination (Table 2).

Under strategy B (n_b =3), the cost per dose was set to $10 and thus the cost per course of vaccination was $30 (=$10*3). With the same target coverage rate of 75%, the total cost of vaccination would be $225,000 (=10,000*0.75*$30), representing 112.5% of the vaccination budget. Thus, there would be insufficient budget (a shortfall of $25,000). This shortfall implies that the budget would have

Table 2 Modelled outputs

Using the input variables shown in Table 1

Output variable	2- dose schedule (strategy A)		3- dose schedule (strategy B)	
	Value	%	Value	%
Number of diarrhoea events expected with no vaccination	3000		3000	
Vaccine cost	$195,000		$225,000	
Vaccine cost as % of available vaccination budget		97.5%		112.5%
Budget shortfall	0		$25,000	
Number of people in target population not covered because of insufficient budget	0		833	
Vaccine efficacy difference		5 %		
Vaccine cost difference				23.1%
Number of people covered by current budget	7500		6667	
Number of diarrhoea events in vaccinated children	900		700	
Number of diarrhoea events in non-vaccinated children	750		1000	
Total number of diarrhoea events with vaccination	1650		1700	
Treatment Cost	$82,500		$85,000	
Gain (reduction in diarrhoea events compared with no vaccination)	**1350**	**45.0%**	**1300**	**43.3%**
Total cost	**$277,500**		**$285,000**	

Additional files

Additional file 1 – Additional-File-1.xls

A copy of the model used for the analysis in this manuscript with the original input values, as a Microsoft *Excel* workbook.

run out with 833 children among the targeted population still to be vaccinated ($25,000/$30 = 833), and thus the available budget would be sufficient to vaccinate 6,667 children. Assuming a vaccine efficacy for the 3-dose schedule of 65%, 700 of the 6,667 children in the vaccinated part of the cohort would still develop diarrhoea, in addition to 1,000 of the 3,333 children in the unvaccinated part of the cohort, yielding a total of 1,700 diarrhoea cases. Thus, the health benefit gained by vaccination using a 3-dose schedule would be a reduction of 1,300 diarrhoea cases (a reduction of 43.3%), compared with no vaccination (Table 2).

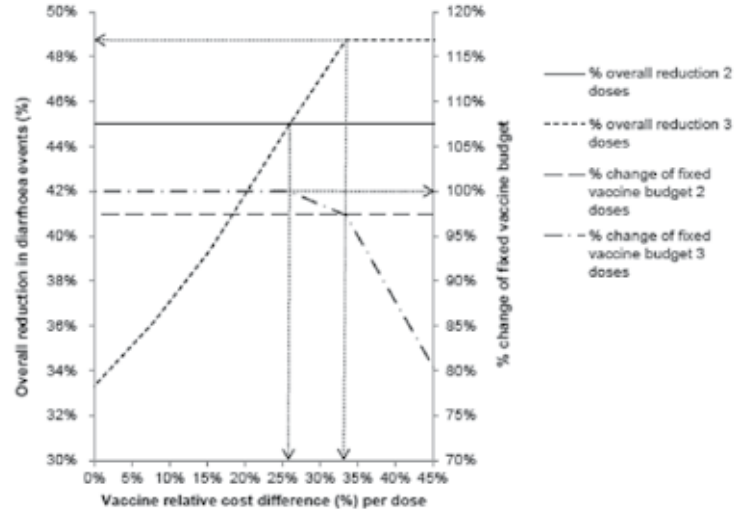
Comparing the two strategies, although the cost per dose was 23% lower with a 3-dose schedule (strategy B), the cost per course was higher ($30 vs $26). The 2-dose schedule (strategy A) was not only cheaper overall ($195,000 vs. $200,000), but also resulted in a greater reduction in diarrhoea events (45% vs 43.3%), despite having a lower vaccine efficacy than the 3-dose schedule. This is because the lower cost per course with the 2-dose schedule would allow more children to be vaccinated within the available allocated budget.

Sensitivity analysis

Figures 1, 2, and 3 show the results of sensitivity analyses for a wide range of values tested.

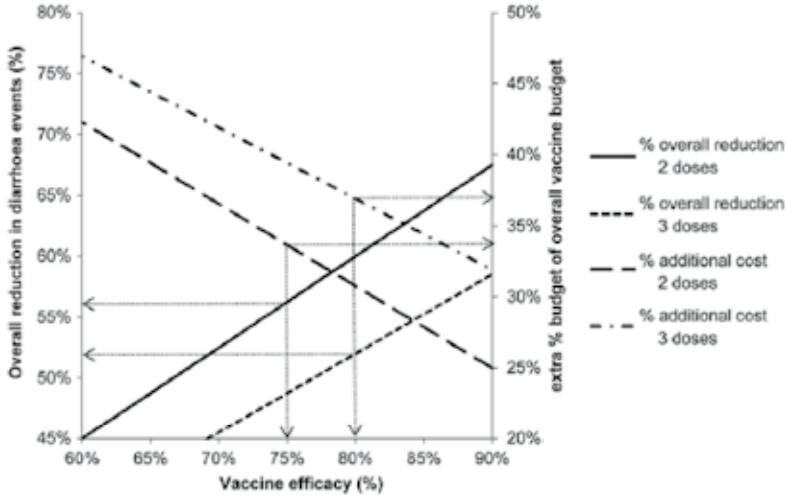
Figure 1 presents the relationship between price per dose and the reduction in diarrhoea events and the total cost of vaccination under the assumptions listed

Figure 1 Effect of the difference in vaccine cost per dose on budget and effect



Reduction in diarrhoea events (left Y-axis) and relative change of vaccine budget constraint (=100%) (right Y-axis) as a function of the relative cost difference per vaccine dose. Assumptions: vaccine budget, $200,000; 2-dose vaccine efficacy (strategy A), 60%; 3- dose vaccine efficacy (strategy B), 65%; target vaccine coverage, 75%; 2-dose vaccine cost per dose (strategy A), $13.00; 3- dose vaccine cost per dose (strategy B), allowed to vary.

Figure 2 Effect of vaccine efficacy on total cost and effect



Total cost (right Y-axis) and effect (reduction in diarrhoea events, left Y-axis) as a function of vaccine efficacy. Assumptions: vaccine budget, $195,000; 2-dose vaccine efficacy (strategy A), 75%; 3-dose vaccine efficacy (strategy B), allowed to vary; target vaccine coverage, 75%; 2-dose vaccine cost per dose (strategy A), $13.00; 3-dose vaccine cost per dose (strategy B), $10.00

in the legend. Consistent with the illustrative example shown in Table 2, with a 2-dose schedule a 45% reduction in diarrhoea events would be observed at a cost of 97.5% of the vaccination budget. Allowing the cost per dose for strategy B to vary, the figure illustrates that a large cost difference per dose of >33.3% would be required before the 3-dose schedule would become less costly; this occurs at the point at which the dash dotted line (– . –) crosses the dashed line (– –). A high cost difference per dose (>25.9% cheaper) would also be required for the 3-dose schedule to achieve a larger reduction in diarrhoea events than the 2-dose schedule; this occurs when the dotted line (...) crosses the solid line. Thus, a 2-dose vaccine schedule would always be the better choice when the relative cost difference does not exceed 25.9%.

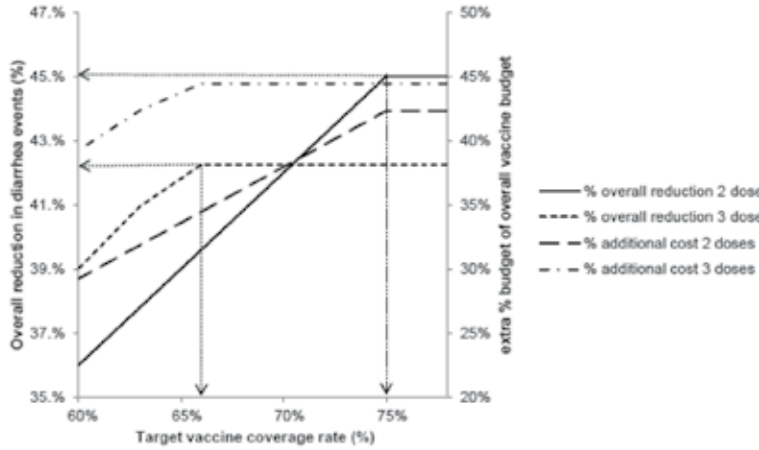
There is a small area between a cost difference per dose of 25.9% and 33.3% where a larger reduction in diarrhoea events would be observed at a total vaccination cost within the fixed budget using the 3-dose strategy, while still remaining at the vaccine coverage rate of 75%. This area varies depending on other factors such as the vaccine efficacy difference. In situations where the 3-dose vaccine is cheaper, no additional reduction in diarrhoea events would be observed above the targeted vaccine coverage rate of 75%.

Figure 2 shows the effect of adding a treatment cost for a diarrhoea event, set at $50 per event, to estimate an overall cost for disease management (vaccination plus the cost of treating cases) with a vaccination cost of $195,000. For example, in Table 2, 1,650 cases of diarrhoea would be expected to occur with the 2-dose schedule, and the cost of treating these cases would be $82,500 (=1,650*$50). The total cost of the 2-dose strategy A would therefore be $277,500 (vaccine cost of $195,000 + cost of treating cases of $82,500). This value is 42.3% higher than the vaccination budget. Thus, under strategy A, assuming a vaccine efficacy of 60% a 45% reduction in diarrhoea events (solid line) could be achieved at a total disease management cost of 42.3% (dashed line) over the vaccination budget. Assuming a vaccine efficacy of 90%, a 67.5% reduction in diarrhoea events (solid line) could be achieved at a total disease management cost of 25% (dashed line) over the vaccination budget.

In Figure 2, it may appear counter-intuitive that a higher vaccine efficacy is needed with a 3-dose strategy versus a 2-dose vaccination strategy to obtain the same overall result. This reflects the higher vaccine coverage rate that can be achieved with a 2- dose vaccine strategy under budget constraint. In addition, the total budget would always be lower with a 2-dose schedule than with a 3-dose schedule when the difference in price per dose is lower than 33.3% (as shown in Figure 1 and discussed above).

Figure 3 demonstrates the effect of target coverage rate on the budget increment and the avoided diarrhoea events. On the left-hand side of the graph, where the target coverage rate is low, there would be sufficient budget for both strategies. Thus, the 3-dose strategy would prevent more cases (due to its higher efficacy) but at a higher cost. The cost for the 3- dose strategy (dash-dotted line) would exceed that for the 2-dose strategy (dashed line) at all coverage rates modelled. However, as coverage increases the number of events prevented by the 2-dose strategy (solid line) would

Figure 3 Effect of target vaccine coverage rate on total cost and effect



Total cost (right Y-axis) and effect (reduction in diarrhoea events, left Y-axis) as a function of target vaccine coverage rate. Assumptions: vaccine budget, $200,000; 2-dose vaccine efficacy (strategy A), 60%; 3-dose vaccine efficacy (strategy B), 65%; 2-dose vaccine cost per dose (strategy A), $13.00; 3-dose vaccine cost per dose (strategy B), $10.00; target vaccine coverage, allowed to vary.

overtake the number of events prevented by the 3-dose strategy (dotted line). This is because the maximum coverage rate achievable within the fixed budget would be higher for the 2-dose schedule (75%) than for the 3-dose schedule (66.7%). Thus, on the right-hand side of the graph where target coverage is high, the 2-dose schedule would prevent more cases than the 3-dose schedule at a lower cost.

DISCUSSION

The results of the modelling exercise presented here indicate that when the vaccination budget is constrained a 2-dose schedule for vaccination against rotavirus infection with the monovalent rotavirus vaccine would be expected to produce a larger reduction in disease events than a 3-dose schedule in most circumstances when using the same vaccine. This reflects the higher coverage rate that can be achieved with a 2-dose schedule than with a 3-dose schedule within a fixed budget. According to the model the 3-dose schedule would produce results superior to the 2-dose schedule only under the following conditions: large improvement in vaccine efficacy for the 3- dose schedule compared with the 2-dose schedule; large reduction in cost per dose for the 3-dose schedule compared with the 2-dose schedule; low target vaccine coverage rate. The effects of these parameters are closely intertwined. So a situation in which the 3-dose strategy would become superior to the 2-dose strategy may be achieved by a large change in one parameter alone, or by smaller changes in several parameters in combination. We will discuss each parameter separately.

A study in Africa reported vaccine efficacy against severe rotavirus gastroenteritis of 63.7% for a 3-dose schedule and 58.7% for a 2-dose schedule [21], a difference

of 5 percentage points. However, it remains uncertain whether adding an extra dose truly improves the overall vaccine efficacy, as 3-dose vaccine efficacy studies using other vaccine products / candidates in low-resource environments have also reported lower efficacy estimates than in wealthier settings [13;14]. The difference in vaccine efficacy in our model was similar to the difference observed in the African study (65% versus 60%). Our results indicated that this magnitude of improvement in efficacy with the 3-dose strategy would result in an overall health gain (fewer diarrhoea events) compared with the 2-dose schedule only with a cost per dose for the 3-dose schedule of at least 25.9% lower than the cost per dose for the 2-dose schedule. The exact value will vary depending on the absolute vaccine efficacy values used, the budget available and the vaccine coverage rate, and thus will vary according to local circumstances. The smaller the gain in vaccine efficacy, the larger the cost difference per dose required.

Vaccine prices are often negotiated according to the total number of doses ordered by a country. An order for 60,000 doses intended to implement a 3-dose strategy covering 20,000 people may vary relatively little in price compared with an order also for 60,000 doses intended to implement a 2-dose strategy covering 30,000 people. Use of a budget optimisation tool may help decision-makers to identify the optimal strategy in their local environment, taking into account any changes in price as well as the expected change in vaccine efficacy and coverage.

The results presented here suggest that a 2-dose schedule is likely to be the optimal strategy, due to a higher vaccine coverage rate that the given budget allows. However, the vaccination budget is not the only factor influencing coverage rates. Other factors may include education, religious beliefs, attitudes to complementary and alternative medicine, gender-based inequity, civil unrest, the percentage of the population living in urban versus rural areas, accessibility of vaccination and other healthcare programmes, and financial factors [22-25]. Such issues are not insurmountable and high vaccine coverage rates can be achieved in low-income countries, as illustrated by high 3-dose diphtheria-tetanus-pertussis coverage rates in Kenya, Bangladesh and Sri Lanka [26]. Other interventions beyond the vaccination programme may be needed to improve the coverage rate, such as health education, better transportation, reduction in communication barriers to vaccinations, outreach to religious leaders and financial incentives.

Many studies have investigated the problem of optimal vaccine dosing schedules. Some have addressed the question from the opposite direction, evaluating whether a smaller number of doses can achieve the same clinical outcomes. For example, a 2-dose-plus-booster schedule for pneumococcal vaccination is accepted as having similar efficacy to a 3-dose-plus-booster schedule [27]. In the present analysis, as the effectiveness of the 2-dose rotavirus vaccine appears to be reduced in low-income countries the relevant question is whether adding one dose could improve clinical results. The strength of the model presented here is that it explicitly recognises the reality of a fixed budget. Adding an extra dose requires increasing the number of doses per vaccinee. Under a fixed budget this either requires an equivalent reduction in price to cover the same number

of people or a corresponding reduction in coverage, or a combination of the two. An optimisation model can explore the question of whether increasing vaccine efficacy by adding an extra dose, or increasing coverage by using a 2-dose schedule, would be the best strategy to maximise the population health gains. It can also quantify the extra budget that would be required to achieve a larger health gain, providing a transparent method of assessing the best strategy for managing disease burden.

The model presented here could be applied to any question about the optimal dose schedule for any vaccine. For instance, the potential switch from a 2-dose to a 1-dose schedule for hepatitis A in Latin America is an important decision that requires careful choice of the optimal administration schedule [28]. The modelling exercise outlined here could provide useful guidance on this question that may be helpful for decision-makers. Additional refinements may be needed, as the present analysis did not use a dynamic model and did not consider the potential effect of an additional vaccine dose on herd protection, or differential waning rates for a 1-dose versus a 2-dose vaccine.

The model is simple in its construction and therefore has some limitations. For example, it does not take account of herd effects which may be important when considering the impact of changes in coverage. The higher coverage achievable with a 2-dose schedule compared with a 3-dose schedule within a fixed budget may lead to greater herd protection and thus to a larger difference in health benefit than estimated in the present model. Furthermore, the model does not cover changes in the timing of doses, effects of disease spread before the final dose, or natural immunity. In the case of rotavirus infection, natural immunity that develops with repeated infections is a competitor to vaccine-induced immunity, leading to a progressive reduction in the scope for vaccination to provide protection over time [29]. The model also does not take account of factors such as logistics and access to healthcare facilities to administer the additional dose[16]. However, in case of working under a fixed budget and increasing the number of doses per person, extra administration cost could be limited as a same person who already received vaccine doses will get an additional one. Things could be dramatically different with the reduction of the number of doses per person. The extra administration cost could then be much higher than in the previous situation because one has to reach additional people (increase the coverage rate) with the extra doses available.

Finally, we opted for a limited perspective in the analysis, namely the health care payer. We thought that essentially these people are most interested in the results when operating under a fixed budget. The societal perspective would only indicate that if a lower vaccine coverage rate was achieved with a 3-dose program, the societal cost could increase.

The optimisation approach here presented is very different from cost-effectiveness analysis. Cost-effectiveness analysis estimates the incremental cost per unit of incremental benefit to calculate an ICER value, and compares it with a threshold value considered to represent acceptable cost-effectiveness. However, to be meaningful

this threshold must be locally defined, taking account of local circumstances. If the threshold is uncertain, the estimated ICER for an intervention may be of limited value in making a decision. Even if the threshold value is accepted, the ICER may not take account of infrastructure expansions required to implement an intervention. For example, a vaccination programme requiring a large increase in cold-chain capacity could be challenging for low-income countries, which in turn could result in a delay to vaccine introduction with consequences for expected health outcomes. Furthermore, an intervention requiring a substantial increase in expenditure – as may be likely with mass population interventions such as vaccination – may exceed the budget available, in which case it may be impractical to implement no matter how favourable the ICER.

The biggest difference between a cost-effectiveness analysis and an optimisation modelling is that in the latter it can take into account the coverage rate as an important variable to reach a certain health goal. In a cost-effectiveness analysis with a static model the vaccine coverage rate may not influence the ICER per se. This is different for a budget impact analysis where the vaccine uptake expressed through the coverage rate will impact the budget cycles. However budget impact analysis only informs about the financial spread over time and is not particularly linked to the goal or objective to be achieved within a defined period as optimisation modelling is pursuing.

Optimisation modelling, as presented in the exercise here, is clearer and simpler to understand [19]. Instead of a threshold value, it identifies the strategy that offers the largest health gain (in the case of a preventive intervention, the lowest number of disease events) within a fixed budget. This more closely reflects the reality of healthcare decisions. The number of available healthcare interventions continually increases, yet national healthcare budgets are not unlimited. It can be applied to simple problems such as the comparison between a 2-dose and 3-dose schedule for rotavirus vaccination illustrated here, or more complex issues such as human papillomavirus vaccination [20]. We may even consider the assessment of different vaccines against different diseases in order to prioritize their indication within a clear budget and time frame such as a multi-year vaccine portfolio management program[30].

Further research will be valuable to refine the simple model described here to take account of more complex issues such as herd protection effects or multi-criteria decision analysis designs.

CONCLUSION

Optimisation modelling indicates that within a fixed budget and for the monovalent rotavirus vaccine, a 2-dose vaccine schedule would be expected to provide better health outcomes in most circumstances than a 3-dose schedule. The model can be used to quantify the conditions of changing dose schedules that would be optimal for any vaccine. It is a more transparent and powerful technique than the more conventional cost-effectiveness analysis for evaluation of the economic questions faced by decision-makers, because it explicitly recognises the budget constraint that is a reality in most healthcare systems around the world.

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THE IMPACT OF ROTAVIRUS VACCINATION IN EGYPT ON LONG-TERM GOVERNMENT EXPENDITURE: A LIFETIME NET TAX ASSESSMENT

Mark Connolly[1, 2], *Oleksandr Topachevskyi*[3], *Baudouin Standaert*[3], *Omayra Ortega*[4], *Maarten Postma*[1]

[1]University of Groningen, Groningen, The Netherlands; [2]Global Market Access Solutions, St-Prex, Switzerland; [3]GlaxoSmithKline Biologicals, Belgium; [4]Arizona State University, Phoenix, USA

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ABSTRACT

Background**:** We evaluate national rotavirus (RV) immunization program costs to estimate how resulting changes in morbidity and mortality will influence government fiscal accounts over time. The assumption being that increased childhood survival in vaccinated cohorts leads to increased numbers of children consuming government resource, and an increased number of future tax payers.

Methods**:** The model framework adopts the Egyptian government perspective for RV immunization costs and all government transfers (eg: education costs, health costs, pensions). To reflect the government tax revenue we applied a fixed income tax burden to earnings over the lifetime of vaccinated and unvaccinated cohorts. At each year of the model we derive net taxes (gross taxes less transfers) discounted to the immunization year to reflect the present value of investment costs.

Results**:** Lifetime discounted cash flows for RV vaccinated and unvaccinated birth cohorts are LE 62,666 million and LE 62,627 million, respectively, at year-25. At year-50 net tax revenues were LE 274,149 million and LE 273,765 million for vaccinated and unvaccinated cohorts, respectively. The internal rate of return for government based on RV vaccination at year-25 and year-50 was 10.6% and 14.9%, respectively. Within the first five years of vaccination small health service cost-savings were achieved attributed to reduced RV-related gastroenteritis cases.

Conclusions**:** The government perspective is useful for evaluating investments in RV vaccination because of ongoing government transfers and tax receipts attributed to changes in RV attributed morbidity and mortality. Using this approach we illustrate both short-term cost advantages, and long-term economic advantages attributed to RV vaccination.

BACKGROUND

Investments in health have shown to be one of the most important human capital determinants that influence economic growth and development, of which vaccines likely play a significant role [1-3]. Previous analyses have estimated an internal rate of return from investments in vaccination programs ranging between 12% and 18% [1;2]. Investments in vaccination not only save lives, reduce suffering, and contribute to economic growth, but they also lead to direct savings in healthcare costs worth millions of dollars every year [3]. Recognizing the important public health benefits and economic advantages of vaccination

programs, the WHO has included vaccines against communicable diseases in the list of essential medicines [4].

The economic beneficiaries of improved health are worth considering in the context of health investments. In most cases the individuals themselves and society as a whole will benefit from improved health. This is attributed to several factors including wage increases, and indirectly through improved educational opportunities influencing future earnings [1;2;5]. Additionally, governments can also be influenced by population health, whereby poor health has the capacity to increase government expenditure in health care and social programs as well as reduce tax-receipts from fewer individuals working [6]. Conversely, the same would be true as economies expand because of improved population health, all things equals, governments will receive more tax revenue [7]. The above observations suggest that it may be in the interest of governments to think carefully about healthcare expenditure to optimise economic growth and sustaining public finances [8].

Vaccination programs can positively influence macroeconomic and microeconomic parameters. Meanwhile the analytical framework commonly used to value health technologies including vaccines mostly ignores the relationship between health investment, human capital, and the economy overall [9;10] Rather emphasis is placed on cost-effectiveness analysis where outcomes are expressed using quality-adjusted life years (QALYs) that have a questionable, tangible economic value. A recent review has summarised the weakness of the frameworks normally used for valuing vaccines citing outcome-related productivity gains, behaviour-related productivity gains, and community externalities are often unaccounted for in the evaluations of immunization programs [11] This is particularly relevant to economic studies of rotavirus (RV) where indirect costs can represent 25–80% of total RV costs [12].

In the developed and developing world RV poses a significant humanistic and economic burden, however they are different. There are more health care costs and fewer deaths in the developed world. But the annual deaths in children ≤5 years of age worldwide caused by RV infection are estimated to be 352,000–592,000 per year, with significant economic consequences [13;14] Considering the high mortality and resources used to treat RV gastroenteritis, it is likely that changes in RV attributed gastroenteritis epidemiology will have significant economic consequences. In this study we explore new investment in RV prevention strategies considering two perspectives: (1) societal and (2) governmental. The underlying premise of the governmental perspective is that changes in RV related morbidity and mortality will increase the number of children utilising government resources, as well as increased numbers of working adults, and future tax payers.

Investments in vaccines offer both short and long term economic benefits. Furthermore, the benefits will accrue to different elements of society depending on the time period considered. For example, in the short-term, families and the health service are likely to benefit from reduced RV attributed gastroenteritis.

However, over time, the government more broadly can benefit from increased survival, increased working-aged populations increasing numbers of tax payers. To reflect how the economic perspective changes over time we construct a model that considers both the governmental perspective, and the societal perspective based on RV vaccine investments. The analysis described here is a continuation of a previously reported economic analysis that evaluated healthcare costs in Egypt attributed to RV vaccination from the health service perspective [15]

MATERIALS AND METHODS

RV vaccination has been shown to saves lives; therefore we sought to estimate how lives saved can influence future government expenditure on social programs such as health, education, and pension costs, as well as influencing future tax receipts. This is referred to as the "government perspective" analysis and requires constructing a model that reflects the life course of average Egyptian citizens taking into consideration average schooling, employment, marriage, wages, pension costs, etc. The model was also constructed to reflect the societal perspective.

To reflect the government and societal perspectives we combine three modelling approaches. Namely, budget impact analysis of RV health costs, human capital modelling based on lives saved and lost productivity, and generational accounting which accounts for a range of other government fiscal transfers to citizens such as education, non-RV health costs and pension costs [16-18] The integrated modelling framework allows us to consider ongoing costs that arise from saving lives attributed RV vaccination, as well as the future tax-receipts attributed to children that would have died in the absence of vaccination. Within this framework, lives saved from the government perspective are not only a cost, but also a future revenue source.

Model design

The model considers hypothetical RV vaccinated and unvaccinated birth cohorts [19]. For each cohort, the costs and consequences associated with differences in RV related gastroenteritis were estimated. Considering the high RV mortality in Egypt for children <5 this approach was deemed appropriate for comparing RV investment costs that influence birth cohorts.[14] Furthermore, the approach allows for comparing the average life course of children receiving RV vaccination with the life course of cohorts without vaccination to evaluate RV investment costs versus no vaccination. Annual adjustments to the birth cohort for RV specific deaths between ages 0–5 year are made based on local epidemiology, and non-RV related deaths from ages 0–100 based on existing life table data [20].

In contrast to most budget impact models that typically complete the analysis five years post-vaccination [21], we attempted to account for ongoing government transfers attributed to vaccinated and unvaccinated cohorts by extending the analysis for 72 years, the average lifetime of an Egyptian citizen. This is particularly relevant considering the survival benefits attributed to RV vaccination. From the surviving vaccinated and unvaccinated cohort we estimated government transfers

for education and health expenditure up until the average age of starting work in Egypt at age 15. Throughout the lifetime, per capita expenditure on education and health is used to estimate the economic impact of vaccinated and unvaccinated cohorts on government accounts.

Rotavirus epidemiology

We calculated incidence rates for children 0–3 years old based on data collected in 4 areas; Abu Homos, Benha, Cairo, and Fayoum, which represent a mix of rural, urban, and sub-urban settings and reported previously [22]. The peak incidence of infection occurs at approximately 10 months of age, which falls within the reported range for the worldwide average peak incidence of between 4 and 36 months [23]. The average incidence for this period was calculated to be 0.19 episodes per child-year. The probability that RV related death would result in children less than five was 0.0018 estimated using a combination of local data and published methodology [24].

Health costs

The costs attributed to non-fatal RV cases were accounted for in the model based on previously reported care-seeking behaviour and treatment costs in Egypt [15]. The costs of care were applied to four different RV health states and treatment scenarios: (1) no treatment; (2) outpatient treatment; (3) hospitalization; and (4) death. Cost of care was based on actual costs accrued by the patients at two hospitals, Benha and Abu Homos, that participated in previously described studies [15] The average cost of hospitalization due to RV, 102 LE, at these two hospitals was used since the former is rural and the latter is peri-urban and Egypt has an even mix of these treatment centres. Both hospitals calculated the same average cost for outpatient care of 23.3 LE. Every year following RV we accounted for healthcare costs, inflated from the base year to derive the rotavirus budget impact similar to the approach used by other authors [12;21].

Costs attributed to non-RV related health costs over the lifetimes of the RV vaccinated and unvaccinated cohorts were also included in the analysis. The model utilises per capita government costs to which we apply a standard function to account for lower healthcare expenditure in younger ages and higher expenditure in elderly persons. Costs in the base year were LE127 based on 1995 estimates and inflated every year in the model. However, previous studies have noted that per capita investment costs have not increased significantly over past decade [25;26]. The impact of growth in public health costs were assessed in the sensitivity analysis.

RV coverage and efficacy

In the analysis it was assumed that RV vaccination would be administered within the existing national immunization program because RV can be piggy-backed onto the current Diphtheria, Pertussis, and Tetanus and (DPT) vaccination schedules. Costs are based on two dose administrations delivered within the first year of life. Similar to the model described by Ortega *et al*, we assume vaccination of the birth cohort of 1,909,000 children in the first year with 98% coverage. No

adjustment for early mortality was made so this likely over estimates vaccination costs as a proportion of children would have died before being vaccinated. The impact of vaccination acquisition costs is explored in the sensitivity analysis. RV efficacy was based on previously published studies [27], and estimates applied in previous Egyptian modelling studies [15]. The vaccine price for two injections used in the base analysis was LE154 with low price (LE98) and high price (LE210) points assessed in the model.

Wages and taxes

The human capital component of the model uses the combined male/female age-specific wages applied to vaccinated and unvaccinated survivors over their working life (age 15–65). Consistent with the generational accounting methodology wages are inflated over time based on increases in productivity. Earnings are adjusted based on current unemployment rates in Egypt and held constant over the lifetime of the model. Information on average earnings is obtained from the Egyptian Central Agency for Mobilization and Statistics (CAPMAS). The unemployment rate currently approximately 9% is held constant over the lifetime of the model [28].

Based on current income tax bands and tax receipts a fixed proportional tax burden of 12% was applied to earnings in the vaccinated and unvaccinated cohorts [29]. An adjustment for tax compliance of approximately 65% was performed [30]. To reflect the possibility that RV may disproportionately affect those from lower socioeconomic groups, and consequently lower wages and tax compliance, we performed a sensitivity analysis based on lowering tax compliance to 20%. Applying a fixed tax burden to salaries likely underestimates total tax burden. Income tax only represents 15% of total government revenues and ignores consumption taxes, stamp duties and other levies [29]. Average weekly wages for public and private workers are LE327 [28].

Public Pensions

Public pensions costs based on 90% coverage were applied at retirement aged. Public pension benefit was calculated to start at age 60 years for RV vaccinated and unvaccinated cohorts based on current pension benefits and inflated over time [31].

Productivity losses

The societal cost was reflected by accounting for time off work for parents based on average wage rates [28] Consistent with previous investigators, we assume two days lost productivity for the parent per RV case [32;33]. Lost productivity costs are only applicable in the first year five.

Discounted net taxes

Every year after birth the model estimates age-specific government transfers and age-specific gross taxes for vaccinated and unvaccinated cohorts. At every age the difference between gross transfers and gross taxes are used to derive discounted net tax contributions. The valuation method is based on discounted cash flows to estimate the attractiveness of an investment based on the present value of the investment and resulting financial consequences attributed to the investment.

In the early stages of life RV vaccinated and unvaccinated cohorts are net recipients of government transfers and tax contributions are zero, consequently the net tax is negative. From the age of birth to commencing employment, the accumulated net taxes remain negative. As the child ages and enters working age gross taxes increase and government transfers are negligible. RV vaccine costs are evaluated as an investment costs for government expenditure at year 0 for the birth cohort. To reflect the present value of the investment we calculate the net present value (NPV) of RV investment costs and all subsequent government transfers and taxes over the lifetime of the birth cohort as follows.

$$NPV = \sum_{t=0}^{T} \frac{R_t - E_t}{(1+r)^t} - K_0(t)$$

R_t = Sum of gross taxes paid by cohort
E_t = Sum of age-specific direct government expenditure per cohort over lifetime (e.g., education, healthcare, pension)
r = Rate of discount
T = Life expectancy
K_o = vaccine purchasing costs at birth age (0)

To assess the present value of RV investments costs for government we assess the profitability index (PI) as follows: Present value future cash flows/Initial investment = PI. The standard convention for interpreting PI is that ratios of 1.0 are the lowest acceptable measure, and values lower than 1.0 indicate the project's present value is less than the initial investment. The internal rate of return (IRR) from positive and negative cash flows was also estimated.

Timeframe

In the short-term (5 years) we assess the societal perspective taking into consideration RV treatment costs, and lost productivity of parents caring for children. Over longer time horizons the government perspective is assessed to the average life-expectancy of 72 years to assess the sustained economic effects of RV vaccination.

Results

Annualised discounted societal costs for vaccinated and unvaccinated cohort are shown in Figure 1. From the societal perspective, costs increase in year-1 attributed to vaccine acquisition costs. However in subsequent years, costs in the vaccinated cohort decrease from reduced RV related gastroenteritis direct medical costs and indirect costs associated with improved productivity. From the societal perspective, the net present value (NPV) of vaccinated and unvaccinated cohorts at 5-years was –LE1,334 million and –LE1,269 million, respectively, with an incremental NPV of –LE 65 million. In the first five years of life differences between the societal and government perspective models are minimal; therefore, only societal perspective data are presented.

Table 1 Overview of model framework and costs included

Model approach	Description
Budget impact	Calculated rotavirus specific treatment costs at different levels of the healthcare system. These costs are from the perspective of the Ministry of Health – the centrally funded health service in Egypt.
Human capital	Apply lifetime age-adjusted lost wages to children that die prematurely from rotavirus. Lost wages of parent caring for child with rotavirus also included.
Generational accounting	Estimate financial impact on national accounts in Egypt for vaccinated and unvaccinated birth cohorts.

Table 2 Government perspective discounted net tax revenue for vaccinated and unvaccinated cohorts at three future time points

Years post vaccination	NPV RV vaccinated birth cohort	NPV unvaccinated birth cohort	Incremental NPV	Profitability index RV vaccinated	IRR RV vaccinated
Year-25	LE 62,666 Million	LE 62,627 Million	LE 39 Million	1.14	10.60%
Year-50	LE 274,149 Million	LE 273,765 Million	LE 384 Million	2.33	14.85%
Year-72	LE 262,174 Million	LE 261,810 Million	LE 364 Million	2.26	14.70%

NPV = net present value; RV = rotavirus; LE = livre égyptienne (egyptian pound)

Table 3 Sensitivity analysis government perspective model

	Incremental-NPV Government perspective year-50	Positive incremental-NPV achieved at age
Base case	LE384 million	22
Incidence rate -32%	LE178 million	32
Incidence rate +47%	LE691 million	4
Rotavirus mortality -50%	LE159 million	28
Rotavirus mortality +50%	LE608 million	20
Low price scenario	LE480 million	4
High price scenario	LE287 million	30

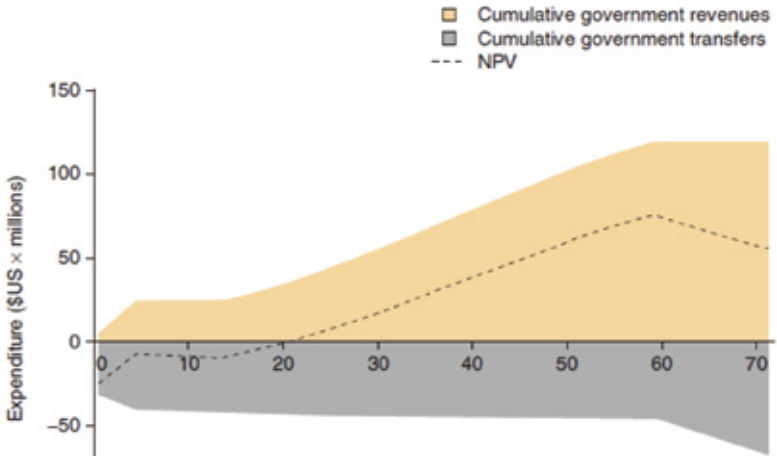
Note: Variance based on data obtained from hospital surveillance studies conducted by collaboration between US Naval Medical Research Unit No. 3 and the Egyptian Ministry of Health and Population; NPV = net present value; LE = livre égyptienne (Egyptian pound)

The lifetime discounted cash flows for vaccinated and unvaccinated birth cohorts are presented for the time horizons of 25, 50 and 72 years (Table II). Discounted net tax revenue from the vaccinated cohort is greater than unvaccinated cohorts with incremental net tax revenues at year-25, year-50, and year-72 of LE28 Million, LE384 Million, and 364 Million, respectively (Table II.).

The profitability index and IRR from the government perspective associated with investing in RV vaccination are also shown in Table II. Under different time horizons evaluated, the profitability index is greater than 1.0 and the IRR at all three time points is greater than discount rate proposed by Egyptian National Bank of 8.5%.

In the government perspective model, the discounted future cash flows associated with implementation of RV vaccine becomes positive after the birth cohort reaches the age of 22 years (Figure 2). At age 22 (payback) all government transfers to the vaccinated cohort for education and health, including vaccination costs, have been

Figure 1 Cumulative government expenditure and tax revenue for vaccinated and unvaccinated cohorts in Egypt with cumulative discounted net present value projected to base year. NPV= net present value



RTV = rotavirus vaccine

paid for by net taxes paid by the cohort. The discounted future cash flow starts to become negative as cohorts retire and draw public pensions at age 60.

Sensitivity analysis

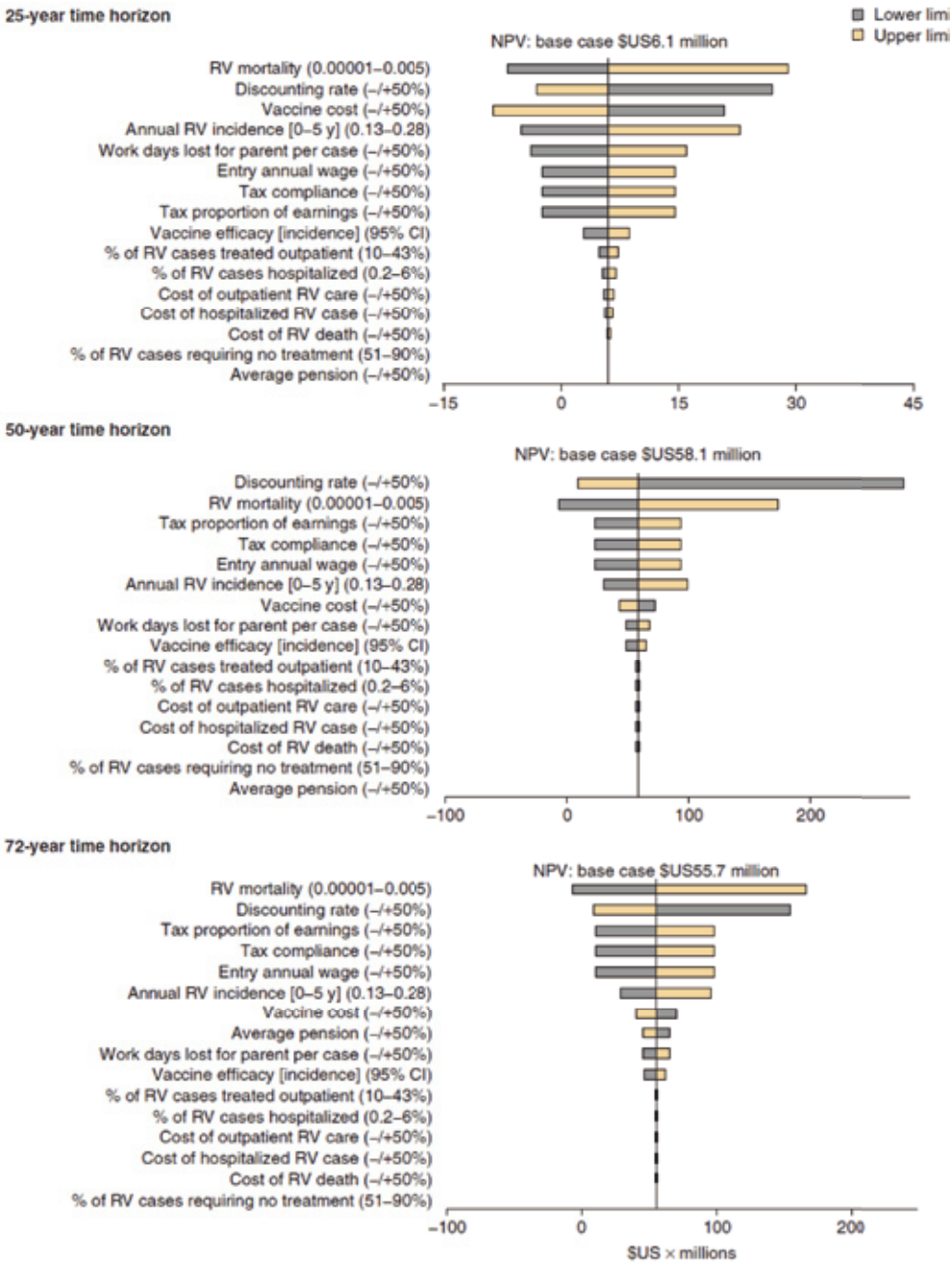
The univariate sensitivity analyses for differences in RV incidence, mortality and vaccine price are described in Table III. In the low price scenario and with increased RV incidence, the NPV for RV vaccination becomes positive at age 4 due to direct and indirect costs saved that cover resources spent on vaccine. Expected NPV under the worst case scenario including reductions in RV incidence, reduced RV mortality and high vaccine pricing, turns positive after vaccinated individuals become 32 years. Under the worst case assumptions individuals need to work approximately 10 years longer in order to offset vaccination costs compared to base case. Altering tax compliance to 20% lowered discounted net tax revenues to LE79,889 million and LE79,821 million in vaccinated and unvaccinated cohorts, and increased the payback age to 35.

DISCUSSION

Few people would dispute the benefits of investing in health and its impact on human capital. Despite the fact that human capital formation is directly influenced by investments in health, the analytical framework often used for evaluating health programs often ignores the relationship between health and human capital. Instead, measurement tools consistent with welfare economics such as health state preferences and health-related quality of life have become the preferred tools for valuing health gains [9].

Generational accounting is an informative tool used by governments to assess the impact of policy changes on intergenerational tax burden [17]. Furthermore,

Figure 2 Time-dependent univariate sensitivity analysis for the rotavirus vaccinated cohort at 25, 50 and 72 years. CI = confidence interval; NPV= net present value; RV= rotavirus



because of mounting fiscal challenges posed by ageing populations in many countries, the GA framework has been advocated for modelling budgetary implications of social expenditure [34]. In this study we employ a modified GA framework to assess discrete investments in health programs to understand the ongoing financial impact of a health investment on government accounts resulting in significant changes in RV morbidity and mortality. While Egypt is not experiencing an ageing population, the consequences of introducing RV could save thousands of children every year that will pose different financial pressures for government. Furthermore, similarly to results obtained with GA, it is important to recognise that the results described here based on investments in RV do not reflect precise forecast of the future. Rather, they reflect a potential fiscal scenario based on prevailing macroeconomic conditions and the interaction of these variables over time [35].

The modelled evaluation suggest that immediately following RV vaccination, vaccine investment costs are partially off-set because of reduced cases of RV attributed gastroenteritis. Although, the cost off-sets and discounted cash flows are not sufficient enough to achieve a positive return on investment from the vaccine costs, over time, as the cohort ages, become educated, and enter the work force, they represent revenue for the Egyptian government through future tax contributions. From the government perspective, RV vaccinated children reach a neutral balance with the Egyptian government based on future government transfers offset against contributed tax receipts at age 22 (i.e. breakeven age), even after adjusting for unemployment and tax non-compliance. At the ages of 25 and 50 the RV vaccinated cohort represents an additional LE39 million and LE384 million in additional net tax revenue compared to the unvaccinated cohort. At age 25 and 50 for RV vaccinated cohorts the internal rate of return of these investments are 10.6% and 14.9%, a rate of return comparable to public investments in tertiary education in OECD countries [36].

The framework described here acknowledges that saving lives through medical interventions represents ongoing costs for government in education and healthcare costs, and that dramatic changes in population health can influence government accounts and economic growth [37] At the margin, our analysis seeks to answer, from the government perspective, whether lives saved by investing in RV will offer a return on investment for the Egyptian government based on future tax receipts attributed to lives saved. The analytical framework discussed here is based on a previously described government investment framework applied to assisted reproductive technology [38].

One of the main arguments against valuing life in economic terms as required with the human capital approach is that it undervalues intangible benefits attributed to changes in health status. Although the use of human capital for valuing health may not be aligned with welfare economic principles, it is an economic reality that keeping people alive will generate ongoing costs for government in direct transfers, as well as economic benefits in the form of future tax receipts [34]. The GA method developed several years ago recognised this fact, and attempted to rationalise

government spending in relation to future revenue and expenditure that are likely to arise from policy decisions. Within the GA framework governments, and specifically treasury departments, recognise that total expenditure is linked to the number of people who demand government resources, as well as the number of people that are helping to finance the system through taxation. In this respect we have attempted to capture the fact that as vaccination programs are introduced they will save lives and these lives will have an impact on government accounts both positively and negatively over time. Those that doubt need only look at how changes in longevity, generous spending and shrinking working-age populations are starting to raise concerns over sustainability of public finances [39]

Since introducing an economic framework to inform resource allocations, considerable debate has focused on the merits of the health service perspective versus the societal perspective to inform decision making [40] In this analysis we circumvent this debate and apply a "government perspective" analysis assessing discounted net tax revenue as the principal economic metric. A government perspective analysing applied to health investments is particularly relevant considering changes in population health can influence government expenditure and tax receipts [6]. Furthermore, considering the proportion public funds used to pay for health services in Egypt as well as many other countries, the broader application of a government perspective analysis is justifiable. Additionally, in light of the established relationship between health and economic growth, a government perspective analysis reflects the fact that any growth attributed to health investments, *Cēterīs paribus,* will result in increased government tax revenue.

Resource allocation decisions in healthcare are challenging, especially in developing countries, because of the need to balance the needs of many with finite resources. Decisions are often based on priorities based on unmet need, burden of illness, fairness, equity and affordability. The research presented here is provocative because it assigns future net tax revenue to discrete investments in RV vaccination. Therefore, it is reasonable to ask how decision-makers should respond to information illustrating the potential economic benefits attributed to resource allocation decisions. We do not expect decision-makers to abandon the core elements of decision-making. Although one of the aims of our work is to highlight the fiscal consequences associated with investments in health. This is particularly relevant in Egypt because increased birth cohort survivorship suggests ongoing costs; however government can also reap financial benefit from previous human capital investments in health and education.

All economic models have inherent weaknesses, and the framework described here integrating three modelling approaches is no exception. Modelling long run economic events requires making predictions about future economic conditions that are certain to change. The simplest approach is to hold variables constant over time and test the sensitivity of those variables likely to influence the results. In this analysis we have shown that decreases in RV infection rates and increased vaccine prices will prolong the payback period for vaccine investment costs. In contrast, increased RV incidence improves the value of prevention because of reduced

consumption of health costs and payback is achieved much quicker. Similarly, reduced vaccine acquisition costs decreases the payback period because it is much easier to offset costs from reduced RV cases when the purchase price is low.

The underlying premise of our analysis is that lives saved through RV vaccination will eventually go on to become average economic citizens in every respect. At the margin the analysis seeks to understand whether discounted net taxes paid by those saved are enough to pay for the RV vaccination. However, some might argue that RV disproportionately affects lower socioeconomic groups that may not achieve normal wage rates in the Egyptian economy which would influence the conclusions described here. Whilst socioeconomic conditions may influence care seeking behaviour for infected children, there is limited evidence to suggest that socioeconomic status is a determinant of RV incidence [41;42]. To reflect the consequences of RV disproportionately impacting lower socioeconomic groups we lowered tax compliance to 20% to account for lower government revenue. This had a dramatic impact on tax revenue; however the vaccinated cohort still achieves a positive return on investment, although the breakeven point was increased to age 35.

Additional criticisms could be levied against the fact that we account for 'per capita' expenditure in every year of life, while also accounting for RV specific costs. Although this does represent double counting of health costs in the year that the event occurs, these costs are trivial in the scheme of all other government costs included in the health investment model described here. To validate this conclusion we did run simulations excluding health costs and noted there was no impact on the model conclusions.

CONCLUSION

The government perspective analysis described here suggests the Egyptian government can achieve both short and long term economic benefits from investing in RV vaccination. We have identified initial cost offsets within the first five years attributed to reduced health services costs from treating RV cases. However, the predominant economic advantages for government are achieved as the cohort of vaccinated children mature and eventually enter the work force and pay taxes. Investments in RV vaccination are offset when the vaccinated cohort of newborns are 22 years of age. This suggests that policy planners need to take into consideration a longer time horizon to enable RV investments to reach maturity.

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