Economic aspects of vaccines and vaccination: a global perspective

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Introduction

A basic principle of economic decision-making is that in an environment of scarce resources choices have to be made in the allocation of these resources. This principle also applies to the provision of health care. The share of health-care expenditures in the Gross Domestic Product (GDP) of most industrialised countries has increased from 3%-5% in the early sixties to 7%-11% in 2001 (from 5% to 14% in the USA) [1] This rise has been attributed to medical advances (increasing the number and technological complexity of medical interventions), population aging, sociological changes (more, but smaller families and less familial support for the elderly) and insufficient productivity increases in the services sector. In less wealthy economies, medical decision-makers are faced with a smaller margin, and such a rise in health-care spending has not been observed yet. Basically, the richer a country, the more it can afford (in nominal and in relative terms) to spend on health care.

The two-way interaction between health and economic development is generally explained as follows. The healthier the population, the more adults can contribute to society by productive activity (i.e., work creating a surplus value in terms of capital gains and human resources), as well as by raising children in a stable environment, thus ensuring continued economic development. The process of economic development itself creates conditions (education, employment, infrastructure (including safe water and sanitation)), which provide a basis for continued improvement in longevity and health-related quality of life [2]. Individual good health can be seen as the product of some unknown complex function to which health care is only one of the inputs. Other important inputs are: life-style variables (eating habits, smoking, etc.), environmental factors (urbanisation, climatic conditions, etc.), income, education and genetic predestination. Furthermore, expenditures on health are not necessarily put to use in the most efficient
way. In this respect a distinction can be made between technical efficiency (providing maximal health care for a given cost, or delivering a certain service at minimal cost) and allocative efficiency (the distribution of resources across alternative services so as to maximise health gains, in accordance with preferences). Finally, though much may be spent on health care, not all people may have equal access to health care of the same quality. Indeed inequities in the consumption of health care may also interfere with the overall allocative efficiency of the system, and create inequities in health per se. Therefore greater expenditures on health care are no guarantee for more global health. It should be noted that these observations do not plead for a reduction or containment of health-care budgets, but rather for a way of spending that ensures that societal goals are met. In order to achieve this, welfare economists focus research on two broad topics: efficiency and equity. Efficiency relates to choosing options that maximise utility from marginal expenditures (i.e., by optimising the production process of health, for which health care is one of the inputs). Equity relates to the fair distribution of all aspects related to health across members in society (e.g., equal access to care). Clearly, there may exist a trade-off between efficiency and equity and giving priority to either of them is a normative issue that should be decided by social and political debate.

Vaccination is undoubtedly one of the major contributors to health improvements in the last three centuries. During this period, the impact of vaccination on longevity is undeniable, despite the fact that its partial contribution is difficult to distinguish from that of improved hygienic conditions and nutrition, and the discovery of penicillin [3, 4]. All of these combined provided the basis for the so-called “epidemiological transition” in industrialised countries. At the same time, infectious diseases remain the main cause of death in many developing countries. Despite the continuing expansion of the vaccine portfolio, implementing financially sustainable basic vaccination programs in poor countries remains problematic. Though this is not so much an economic as a financial aspect, we will return to this issue in the section “Financing vaccines”.

### Peculiarities of vaccination and the vaccine market

A number of peculiar characteristics set vaccination apart from other interventions in health care [5]: (1) Since vaccination is (usually) a form of primary prevention, it intervenes in people (often children) who are generally in good health. But unlike most other prevention programs, the interven-

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1 Epidemiological transition: transition from infectious and parasitic diseases (in children) as the main causes of death to chronic and degenerative diseases of adulthood. This transition evolved parallel to the demographic transition: transition from high fertility and death rates to low fertility and death rates.
tion itself can cause harm to the vaccine recipient, because in rare cases vacci-

cine-associated adverse events (VAAE) occur. This means that people make trade-offs between risks of vaccine-preventable disease and risks of VAAE. The perception of these risks is quintessential to the individual demand for vaccines (if left to free-market mechanisms), and dominates the influence of other factors such as price [6].

(2) Vaccination not only protects vaccine recipients, but it also reduces exposure of unvaccinated people, due to the reduced circulation of the infectious agent (if the transmission of infection occurs from human to human). This is not always beneficial for public health as the reduced risk of transmission leads to an increased average age at infection (with many “childhood” infections being more severe if contracted in adulthood) [7, 8]. Together with the first characteristic, this means that people generally have an interest in having everyone else vaccinated, but not themselves (or their children).

(3) A number of infections can be eradicated in the long run if vaccination efforts are sustained at sufficiently high coverage levels around the world. In other words, sometimes vaccination has the potential of making itself redundant. Choices about eradication are closely linked to the welfare of future generations and societal time preference (see also below) [5, 9].

Since the perceptions outlined above are usually distorted by insufficient or biased information, government intervention (in the form of subsidies, or coercion) is desirable to ensure that vaccine uptake remains optimal. Indeed, as uptake increases the risk of VAAE remains constant, but individuals may perceive it to increase. At the same time the absence of vaccine-preventable disease may create a false sense of security, and lure people into believing that their risk of disease has reduced to zero as well, while this is highly dependent on historical and future rates of exposure and vaccination in the rest of the population.

The vaccine market represents only 1.5% of the global pharmaceutical market, but has high growth potential (estimated at 10–20% per year by various sources, mainly due to new combination, new prophylactic and new therapeutic vaccines) [10]. For a manufacturer, the contribution margins of vaccines are low compared to those of other products in both the developing and industrialised world (due to price and licensing regulations). The few suppliers of vaccines now aim to limit production to the projected global needs in any given year (UNICEF bought about 90% of “traditional” vaccine supply in 2003, compared to about 25% in 1997). Thus the market is very vulnerable to capacity problems: a problem with a single batch of vaccines by a single producer can have severe knock-on effects across the globe. This may also explain why, for some of the old vaccines, the price fluctuates, and has had the tendency to rise over the last 5 years. Close co-operation between demanders (governments or agencies) and suppliers is essential to ensure continued availability at the right time.

Vaccines are supplied under a tiered price system, with 88% of sales volume in developing countries and countries in transition, but 75% of sales
revenue in industrialised countries [10]. It is therefore not surprising that
global vaccine manufacturers (with three big producers (GlaxoSmithKline,
Aventis and Merck) occupying 77% of the global market) tend to focus on
products for the industrialised world.

It is to be expected that more combination vaccines will become avail-
able and existing combinations extended. Examples of this include the
hexavalent diptheria-tetanus-pertussis-inactivated polio virus – Haemo-
philus influenza type b – hepatitis B (DTP–IPV-Hib–HepB) vaccine, and
the quadrivalent measles-mumps-rubella-varicella-varicella-zoster (MMRVZ) vac-
cine. The research and development costs for these vaccines are high due to
technical and regulatory complexity. The technicality, the multiple patents
and requirements in terms of clinical trials (all demanding great time and
money investments) increase barriers to enter the vaccine market. This may
lead to more monopolistic behaviour, with risks to supply, choice and price.

Clearly, the benefits of combination vaccines are many. For instance, reduc-
tions in the number of injections and associated administration costs
(including reduced money, time and pain costs for children and their par-
ents), and reduced transmission by contaminated needles benefit recipients
and the public health bodies. Free-rider effects (important and not-so-
important vaccines can hook up with established vaccines, irrespective of
how recipients perceive their importance) and economies of scope² benefit
manufacturers and perhaps public health bodies. These benefits will have to
be traded off versus the higher price of combination vaccines.

Because governments, health insurers or agencies (UNICEF, PAHO)
typically buy vaccines directly from producers, there is also little diversity
on the demand side of the market. All of this implies that there is little com-
petition on both sides of the market and that global societal goals (devel-
opment and supply of affordable vaccines for poor countries as well as rich
countries) are unlikely to be met by relying entirely on free-market mech-
anisms (particularly since these are hampered by (necessary) regulation
with regards to quality control and licensing).

Economic evaluation as an aid to decision-making

Concept

By using economic evaluation we are essentially trying to answer the fol-
lowing questions [5]:

² Economies of scope are similar to economies of scale, but rather than referring to efficien-
cies of changes to the scale of the output of a single product, economies of scope refer to
efficiencies of changes to the scope of marketing and distributing a range of products (com-
bination vaccines are an example of product building).
1) Is the vaccination program under study worth doing compared to alternative ways of using the same resources? In other words: should the (health care) resources be spent on such a vaccination program, and not on something else?

2) More specifically, if we are deciding to vaccinate against a particular disease, whom should we vaccinate, at which age, with which vaccine and how should the vaccine be delivered and administered in order to deploy our scarce resources in the most efficient way?

Most economic evaluations of vaccination are model-based, because the alternative, empirical analysis, is usually impractical, very time-consuming (for most vaccines it takes decades for the full effects to unfold), very expensive and potentially unethical.

A complete economic evaluation should compare different options for an intervention, in terms of economic costs as well as health consequences. There may be several options to prevent an infectious disease, some of which are mutually exclusive, while others are complementary. The relevant costs and benefits need to be collected for each option, and calculated relative (incremental) to another option. The choice of the reference strategy against which the other options are evaluated can be highly influential for the results of the evaluation. Unless it is a cost-ineffective strategy, current practice is the preferred strategy of reference. When a new vaccine is introduced, the reference strategy is often referred to as “doing nothing” (no vaccination), although in this case “doing nothing” usually means the treatment of cases as they arise, with the corresponding public health measures.

**Perspective: costs and benefits for whom?**

A generalised distinction between the costs and benefits of vaccination is presented in Table 1. The intervention costs dominate the cost side. These are the costs necessary to implement the vaccination program. Additionally there are costs incurred to receive the vaccine. The benefits of vaccination are the gains in health and the avoided costs. Direct costs can be avoided because less treatment is needed for curing or nursing the disease against which the vaccination program is aimed. Additionally indirect costs can be avoided because vaccination may partly prevent people having to interrupt their normal activities in society because of their illness or the illness of their relatives.

From the health-care payer’s point of view, only direct medical costs need to be taken into account. However, from society’s viewpoint, indirect non-medical costs are also relevant. Other viewpoints can be those of patients, hospitals, travel clinics, insurance companies, employers, etc. (see Fig. 1). For each of these perspectives different costs and benefits may be
relevant. This implies that it is possible for an intervention to be relatively cost-effective for one party involved, while it is not for another.

Different cost categories are listed in Table 2. The listings in italics are often not taken into account, because they can be relatively small in comparison to the other costs and/or because they are difficult to estimate. Sometimes their inclusion is not relevant to express the viewpoint of the analysis. However, if they are relevant for the viewpoint of the analysis, their impact on the results could be tested in a sensitivity analysis and their existence should be mentioned when the results are presented.

Some diseases affect expectations and behaviour beyond one degree of separation from the pathogen. For instance the global impact of the SARS outbreak in 2003 was modest in disease burden (8098 probable cases, 774 deaths) and associated health-care costs, but it had an impressive impact on the global economy (US$30–100 bn, or $3–10m per case) in macro-economic terms (when the impact on consumption and investments are considered) [11, 12]. A similar situation could arise for pandemic influenza, or any other disease that affects risk perceptions of consumers and investors (e.g., variant Creutzfeld Jacobs Disease). However, for most currently vaccine-preventable diseases, micro-economic evaluation would provide an appropriate analytical framework, preferably adopting a societal perspective. In reality, decisions about universal vaccination are often taken from the perspective of the National Health Service (NHS) or the Ministry of Health and at best from the health-care payer’s perspective (which in addition to the NHS costs also includes direct co-insurance and co-payments by the patient). Indeed, decision-makers in health care tend to focus primarily on direct costs since these are most indicative of their immediate budgets, even if their decision has bearings on society at large.

### Opportunity, average and marginal costs

When it comes to estimating unit costs or prices, it should be noted that costs in an economic sense are opportunity costs: they represent a sacrifice of the next best alternative application [13]. This entails that costs in an eco-

| Costs                                      | Benefits                                      |
|-------------------------------------------|-----------------------------------------------|
| Direct costs (mainly intervention costs)  | Avoided direct costs (mainly treatment costs) |
| Indirect costs (mainly time lost to receive vaccination) | Avoided indirect costs (mainly time gained by avoiding illness) |
|                                          | Health gains (physical and psychological)     |

Source: [5]
nomic sense are not necessarily the same as financial expenditures, and that they can also represent goods and services that are not expressed in monetary terms. However, market prices are often used as a proxy. If particular goods and services are not traded on a market, ("shadow -") prices of a similar activity can be used instead. For example, work of volunteers can be approximated by wages of unskilled labour. Similarly, patients’ leisure time could be based on average earnings or average overtime earnings. Average costs per unit of output are the total costs of producing a quantity divided by that quantity. Marginal costs constitute the additional costs of producing one additional unit of output. Since decisions are made at the margin, marginal costs should be used where they are substantially different from average costs [13]. For vaccination, this distinction is most relevant for estimating the costs of the program [5]. The costs of adding a particular vaccine to the existing program depends on how well the schedule of the new vaccine fits in with the other schedules, whether specific precautions need to be taken, whether potential vaccinees need to be screened prior to vaccination or whether a specific target group is envisaged. The costs that are most heavily affected by adding a new vaccine to the existing program are the variable costs of the program (time spent per vaccinee, number of vaccines bought, etc.), whereas the influence on the fixed intervention costs (buildings, general equipment, etc.) is usually small (unless a new vaccine requires a substantially different infrastructure in terms of storage and transport). A good example of this is provided by Hall et al. who examined the immunisation program in The Gambia (more recently these results were confirmed by a similar analysis in Addis Ababa, Ethiopia) [14, 15]. They found that the additional costs of adding hepatitis B vaccine to the existing Expanded

Figure 1. Perspective: different costs (and effects) may be relevant for different analytical viewpoints
Program on Immunisation (EPI) vaccines (measles, polio, DTP and Bacille Calmette-Guérin (BCG)), would be for 94% recurrent costs (of which 87% for purchasing hepatitis B vaccine (hepB)). Still, the introduction of a new expensive vaccine could more than double the costs of the program in some countries because of its sheer price compared to other vaccines in the program.

Valuing health outcomes: different types of economic evaluations

The main objective of vaccination is to prevent disease. The most important benefits from a public health point of view are therefore the health gains (see Tab. 1). These are both physical (avoiding illness, suffering, mortality, etc.), and psychological (avoiding distress, anxiety, etc.). Specific vaccine-related psychological health gains include the general feeling of well-being and security of vaccine recipients from knowing that they are protected against disease. This could evidently lead to behavioural changes (e.g., a vaccine against HIV/AIDS could have a large influence upon the sexual behaviour of vaccine recipients).

The valuation of health outcomes has far-reaching consequences for the methodology and study design of applied analyses. Generally, a distinction is made between four different methods, depending on the way in which health gains are measured [13].

A cost-minimisation analysis compares the costs of equally effective alternatives, without quantifying the health gains. It differs from a pure cost
analysis in that there is always more than one option analysed and that the effectiveness of the different alternatives is known to be equal.

In a cost-effectiveness analysis, health gains are measured in one-dimensional natural units (e.g., infections prevented, hospitalisations prevented, deaths averted, life-years gained…), implying that only one aspect of effectiveness is considered (e.g., postponing the time of death) and other related aspects are not (e.g., the quality of life). The results of cost-effectiveness analyses (CEA) are usually presented as a ratio. A Cost-Effectiveness Ratio (CER) is a measure of the incremental costs, which are necessary to obtain one unit of a health gain by implementing a strategy \( j \) instead of a strategy \( i \) (expressed in incremental costs per life-year gained, incremental costs per infection prevented, etc.).

\[
\text{CER} = \frac{\text{Costs with strategy } j - \text{Costs with strategy } i}{\text{Effects with strategy } j - \text{Effects with strategy } i}
\]

The lower the ratio, the more efficiently strategy \( j \) gains health compared to strategy \( i \).

The units in which health gains are expressed should represent the final results or clinical endpoints of an intervention as adequately as possible, in order to enable comparison between different interventions [16]. If hypothetically, the cost-effectiveness of hepatitis B vaccination were $50 per infection prevented, whereas Hib vaccination is estimated at $50,000 per infection prevented, it is wrong to conclude that hepatitis B vaccination is more cost-effective (because it is less costly to prevent one infection). To make that judgement, the avoided effects would need to be expressed in a more comparable endpoint, like life-years saved. To make the comparison even more relevant, different health states should be weighed by their quality (scaled from 0 (meaning death) to 1 (meaning perfect health)). This approach is used in cost-utility analysis (CUA), where health gains are measured in Quality-Adjusted Life-Years (QALYs) saved or another combined measure of morbidity and mortality (e.g., Disability-Adjusted Life-Years (DALY)). A Cost-Utility Ratio (CUR) is similar to a CER, except that the denominator contains the difference in QALYs (or DALYs), instead of the difference in natural units, such as cases avoided or life-years gained. The main advantage of CUA over CEA is that it allows comparison of very different health-care interventions, for instance, those that predominantly extend lives (e.g., flu vaccination of the elderly) with those that improve the quality of life (e.g., drugs against erectile dysfunction).

In Cost-Benefit Analysis (CBA), the health gains are converted into monetary units, which, in theory, allows the many dimensions that are associated with an improvement in health status (over and above the length and health-related quality of life) to be included. There are benefits beyond the health outcomes such as information, caring, regret, anxiety reduction, communication and process utility (benefits from health-care use). Further-
more, option value (i.e., benefits derived from needing care in the future) and non-use value (i.e., externalities related to caring for the health of others) can also be (potentially) elicited [17]. The results of a CBA can be presented as the difference between costs and benefits (the net costs (or net savings)) or as a ratio. The benefit-cost ratio (BCR) expresses to which extent an investment in an intervention can be recovered by the consequences of that intervention (expressed as a unitless number or a %).

Cost-benefit analysis allows for comparisons between totally different projects in society (e.g., comparing a vaccination campaign with the construction of a new bridge). When budgets are very limited and many urgent interventions compete, as in developing countries, such cross-sector comparisons may actually be used in practice. Clearly, the potential of CBA to make such comparisons possible is a major advantage to aid decision-making.

The strength of CBA in theory, i.e., the explicit monetary valuation of health gains, has up till now been also its weakness in practical decision-making. In theory it seems preferable that the valuation of health gains (and of life) is done in an explicit, transparent and representative way as in CBA, instead of the implicit, inconsistent and arbitrary way it is often done in today’s decision-making. However, in a health-care environment the monetary valuation of health (and particularly of life) is often rejected on an emotional basis3 [18]. Additionally, economists have few credible arguments to counter these objections, as the current methods which place a monetary value on health (human-capital and willingness-to-pay methods) can hardly be called consistent and reliable in practice [19–21]. In view of this, most economic evaluations in health care are based on CEA or CUA. The literature on these has increased exponentially since the 1980s, for vaccines at least as much as for other interventions in health care, underlining the importance of a sound theoretical framework for these analyses [17].

**Time preference**

Individuals (and societies), in general, prefer to receive benefits as early as possible and incur costs as late as possible. This so-called time preference means that the same amount of wealth or health would have a different value to a decision-maker in the present, if this amount is gained at different points in time. Note that time preference has nothing to do with inflation. A vaccination program is an investment made in the present (i.e., the costs of buying and administering vaccines) to gain benefits spread out over the future (i.e., avoided costs of treatment, avoided morbidity and mortalit-

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3 As noted by Mooney [18]: “To be trained in medicine, nursing or one of the other ‘sharp end’ disciplines and then be faced with some hard-nosed, cold-blooded economist placing money values on human life and suffering is anathema to many.”
Discounting is a technique by which future events (e.g., costs and health outcomes) are valued less the further in the future they arise. The degree to which they are valued less is determined by the discount rate (frequently assumed to be constant through time): the higher the rate the less future benefits and costs are valued. Although there is general agreement on the discounting of costs, the arguments for discounting non-monetised health outcomes are contradictory [5]. Discounting costs without discounting benefits leads, amongst others, to the paradoxical situation that any eradication program will yield infinite benefits [13]. This would imply that all current resources should be spent on research of eradicable diseases, and the implementation of eradication programs, and not a single penny on cure. Such paradoxes, and the observation that individuals generally have a positive discount rate for health, clearly indicates that health too should be discounted at a positive rate. But there is no general agreement on how the discount rate for health should compare to that of wealth. There are arguments to apply an equal discount rate to both costs and health effects [22, 23]. The underpinnings and relevance of these are questionable, so that a lower discount rate for health effects than for costs has also been proposed [24, 25]. Because of the very long time spans over which benefits accrue, the analysis of most vaccination programs is very sensitive to discounting (of costs as well as health effects). Nonetheless, this is no cause for a different approach to discounting for vaccination. Still, further empirical research is needed to strengthen or to change the basis for conventional discount rates (mostly 3%, or 5%) and discount models (mostly stationary) [5]. A slight decrease in discount rate (from, say, 5% to 3%) could change the cost-effectiveness of some vaccination programs from unattractive to attractive. Also, it is likely that time preference in developing countries is substantially different (i.e., higher) from that in industrialised countries, particularly for those countries that have decreasing health (e.g., life-expectancy due to HIV/AIDS) or wealth (e.g., real GDP) expectations [5].

Decision-making: are vaccines a good buy?

In theory, decisions are made by interpreting the results of economic evaluation as follows. In Figure 2 a new program is plotted in terms of costs and effectiveness versus the reference strategy in the origin. If the new program is less costly and more effective than the reference, then the new program (a “dominant” strategy) should be implemented. Likewise, if the new program is more costly and less effective than the reference, it should be rejected. In the other quadrants the decision is more complex, because it depends on a value judgement. If the incremental CER (or CUR) is smaller than a given willingness to pay (or threshold cost-effectiveness criterion), “K”, it would be acceptable. The question then is, how to determine K? This could be determined by social debate or by comparing it to what is widely accept-
ed in practice. The most widely cited K in industrialised countries is $50,000 per QALY gained. There may also be a grey zone for K in which some interventions are implemented and others are not (e.g., between $40,000 per QALY gained and $100,000 per QALY gained), whereas under and above that grey zone all and none of the interventions are implemented, respectively. However, the greater the analytical uncertainty and the burden of disease, the more decisions are likely to deviate from such clear cut-off practices [26]. Different societies should have a different willingness to pay, though there are few instances in which societies (or their decision-makers) have tried to determine what the appropriate value of K is. The World Bank has suggested using GNP per capita as a benchmark for K. Note that in CBA, K has already been given an explicit value.

In league tables, many vaccination programs rank with the most cost-effective interventions in health care in industrialised countries [5, 27–29]. It is tempting to try and estimate the global historical value of vaccination. However, due to scarcity of data in most parts of the world such an exercise
would be, by necessity, extremely crude. It seems clear, though, that the smallpox eradication program and the establishment of the EPI have generated enormous benefits, not only by directly protecting against important vaccine-preventable diseases, but also by providing opportunities for health education and infrastructure in developing countries [30]. Yet the associated disease reduction in smallpox, measles and tetanus alone is bound to have been a cost-saving enterprise around the world (i.e., in the lower right quadrant of Fig. 2), currently averting over 8 million deaths per annum, compared to a “never having vaccinations” situation. However, when we are making choices today, we have to consider what additional benefits we will achieve by making additional investments, and this is bound to vary between countries at different stages of economic development, different epidemiologies of disease, and different historical vaccine-uptake levels. Hence data from one country cannot always be simply extrapolated to another.

In practice, there are many factors that come into play when decisions are made about new health-care interventions (see Fig. 3). In a democracy, a decision-maker receives a temporary, renewable mandate from the public to allocate a given budget. That person is well aware of the public perceptions of public health problems, and the impact of decisions thereon. At the same time, pressure groups may try to influence decision-makers or the public’s perception. These pressure groups have vested interests in the decisions (be it as sellers of vaccines, or sellers of services for the cure of vaccine-preventable diseases). Societal goals with regards to the decision can only be met by considering its medical, social, ethical and cost implications. The theoretical foundation of economic evaluation (so-called “Pareto opti-
mality”) addresses efficiency, without concern for distributional aspects (equity). Therefore, economic evaluation combines the medical/epidemiological and cost implications, but does not consider the social and ethical implications depicted in Figure 3 (though in CBA these aspects could theoretically be included, if a willingness-to-pay approach is used, and it is possible to weight quality-of-life gains to help achieve equity goals, as is commonly performed in DALYs). Therefore economic evaluation should be seen as an additional type of analysis that cannot stand on its own in its current form (it is an aid to decision-making, not a decision-maker in itself). At the same time, ideally, the influence of pressure groups, and the public’s perceptions (rather than the public’s true preferences) should be minimised in this process. It is noteworthy that most vaccination programs are likely to be equitable according to prevailing theories of justice [5]. Indeed, an analysis for Bangladesh indicated that socio-economic inequalities in mortality of under-5-year-olds were eliminated by measles vaccination [31].

Financing vaccines

In the past, vaccination interests of poor and wealthy nations seemed more in tune than today. Moreover, the research and development costs of the new generation of vaccines, based on biotechnology, are greater and the regulatory hurdles higher, meaning that new vaccines are much more expensive than the basic package of “traditional” vaccines. The first new expensive vaccine for global use was the hepatitis B vaccine, which became available in 1981. The main reason why it was not immediately included in universal vaccination programs was its price, because initially the hepatitis B vaccine cost more than the other six EPI vaccines put together.

With the advent of more expensive vaccines, the introduction of a new vaccine is not as straightforward as it used to be in the industrialised world. In contrast to some of the “older” vaccines (e.g., measles, pertussis), newer vaccines may not result in net savings to the health-care system. Nonetheless, if considered desirable, industrialised countries have no difficulty in financing the introduction of new vaccines, and ensuring the continuing uptake of old ones. For developing countries, the main difficulty is not so much to determine whether it would be cost-effective to introduce a vaccine, but to ensure that the introduction is financially sustainable. When external donors sponsor vaccination programs the sustainability takes the form of a partnership with shared responsibility and the promise by the receiver of the financing to create the conditions to become self-sufficient in the long run, either alone or by attracting further external funding.

Global immunisation efforts came under pressure as the EPI, which was launched in the 1970s as a way of building on the success of the smallpox eradication program, lost its momentum in the 1990s, and failed to attain the year 2000 goal of 90% global vaccination coverage. Indeed, global child-
hood immunisation coverage against the six main target diseases (polio, DTP, measles and tuberculosis), which was less than 5% in 1974, decreased from about 80% in 1990 to 75% in 2000 [32]. Coverage for the complete schedule of DTP remains well below 75% in tens of developing countries, mostly in sub-Saharan Africa. These countries are traditionally bottlenecks in the EPI because of great financial constraints, the evolution of the HIV epidemic, logistical difficulties, poor governance and general socio-economic conditions (sometimes aggravated by war). As these factors evolved unfavourably in the 1990s, international alliances shifted their efforts from reducing general global inequalities in health (“Health for All”) to more selective strategies, like the polio eradication program and the introduction of new and improved vaccines.

The discrepancy between the developing and the industrialised world is likely to become greater, as private vaccine development focuses primarily on diseases that affect the wealthy. Indeed, only about 1% of world drug sales is for African countries. It has been estimated that of all expenditures on health research (over $70 billion per year), 90% is for diseases that affect 10% of the world’s population [33].

Using recent examples, Kaddar et al. assert that financing vaccination should be affordable by all countries, at least for the basic vaccines [34]. The cost of fully immunizing a child with the basic vaccines is $5 to $25, which typically represents 5% to 10% of public health expenditures, <$0.4 per capita or about 0.1% of GDP. Most vaccination costs are fixed costs of personnel and infrastructure, and the marginal costs of an additional vaccine may often be bearable for the domestic budget (though still highly dependent on vaccine price). As the 20th century drew to a close, the landscape of external vaccine financing underwent dramatic changes with the inception of the Global Alliance for Vaccines and Immunization (GAVI) and the Vaccine Fund, with the aims to stimulate research and development for developing world problems, strengthen immunization systems, and promote and support the introduction of new and underused vaccines. GAVI is an alliance of financiers (development banks, aid agencies, foundations), agencies (UNICEF, WHO), vaccine developers and manufacturers, as well as developing country governments, whereas the Vaccine Fund manages private financial resources, such as those from the Bill & Melinda Gates Foundation, and public contributions from a small number of wealthy countries.

**Conclusion**

The first generation of vaccines, such as measles and oral polio vaccines, was used against common and serious childhood diseases afflicting all countries in the world. Few of these vaccination programs were subject to economic analysis before introduction, and for good reason: the benefits
were obvious and the costs low. Indeed, they were probably amongst the most effective and cost-effective public health programs of the 20th century. This is no longer necessarily the case with new vaccine introductions. New vaccines are generally higher priced and unlikely to fall in price to the level of the first generation of vaccines. Furthermore, they are often aimed at less common or less serious diseases (particularly in the industrialised world). Thus, whether these vaccines are worth introducing is less clear. Vaccine financing has recently changed with important initiatives stimulating development and use of vaccines for the developing world. These are to be welcomed as they may further alleviate the disease burden in developing countries at affordable cost, correct market imperfections with regard to research and development, and reduce inequalities in health. Nonetheless, the introduction of new vaccines demands cautious planning. If it comes at the expense of the uptake of the first generation of vaccines, it may have a detrimental influence on the effectiveness and cost-effectiveness of the whole program. In view of all these developments, the role of economic evaluation in vaccine program design is only likely to increase in the future.

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