



POLICY FORUM: MEDICINE

The Intangible Value of Vaccination

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The introduction of vaccines during the early part of the last century and the introduction of antibiotics and modern hygiene practices a few decades later contributed to the decline of diseases that had been responsible for much of the morbidity and mortality of humans during recorded history. Indeed, vaccination is considered the most effective medical intervention [table S1 (1)], and there has never been a better time than the present for vaccine development and implementation. However, the bitter truth is that the future of vaccination as a preventative strategy is uncertain, and there is not a great deal of enthusiasm about vaccine development among those who actually have the capability to develop and produce vaccines. With the present vaccine shortages in the USA, the panics recently generated by the attack with anthrax and the threat of smallpox are only two examples of our inadequate planning. We believe that a radical change in the economic approach to vaccines and preventive medicine is necessary.

Recent positive approaches to vaccines (Fig. 1) were initiated in 1981 when the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) launched the Expanded Program of Immunization (EPI), which was designed to make the basic vaccines (diphtheria, pertussis, tetanus, polio, and measles) available to more than 80% of children worldwide. In 1983, the World Bank developed the concept that absence of health was a main obstacle to the economic development of poor countries (2) and indicated that vaccination would be a first step to improved economies. This perception of the social value of vaccination made vaccines an ideal target for charities and private and public donors, as in 1940, when the March of Dimes mobilized against polio.

Enthusiasm reached a peak in January

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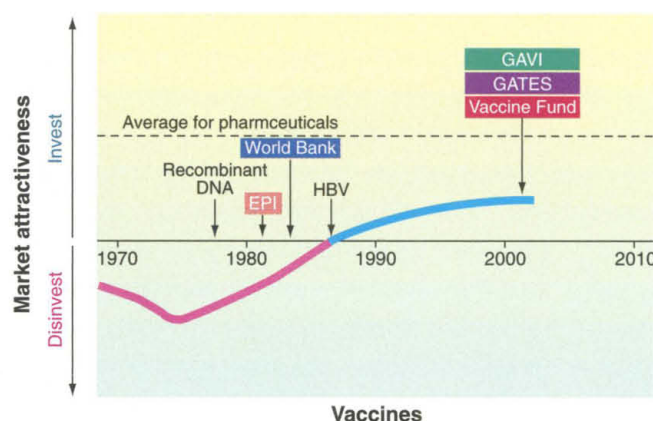


Fig. 1. Historical attractiveness of vaccine investment.

2000, with the establishment of the Global Alliance for Vaccines and Immunization (GAVI), which consolidated public and private efforts with the mission of expanding access to existing vaccines and accelerating development of vaccines needed primarily in developing countries. To achieve this goal, GAVI established the Vaccine Fund, an independent body that raises financial resources. The donation of \$750 million from the Bill and Melinda Gates Foundation was followed by other donations, and the Vaccine Fund today totals more than \$1.1 billion.

However, although vaccines are highly ranked for the implied value they provide to human society (Fig. 2), the economic value associated with them is negligible when compared with that of pharmaceutical drugs. Worldwide, vaccine potential sales are estimated to be approximately \$6.5 billion, which represents only about 2% of the global pharmaceutical market (3), an amount roughly equivalent to the sales of one successful ulcer drug. During the last 40 years, most pharmaceutical manufacturers have not considered vaccines an attractive business opportunity because of their low return on investment and their exposure to legal liability. Since 1967, the number of companies producing vaccines in the United States dropped from 37 to 10. Similar figures apply to Europe. This global deficiency has been temporarily obscured by an unprecedented investment by charities and donations (Fig. 1). However, all this is destined to fail unless we use it to

build a sustainable system for vaccine development and manufacturing.

Part of this decline in production has been caused by well-intentioned people who are well aware of the social value of vaccines and motivated by a humanitarian spirit. They would like to make vaccines available to everybody and believe that a low price would be a solution. Unfortunately, their efforts are counterproductive, because any time they mention that vaccines should have low prices, they provide more incentives to industry to walk away.

The current shortage of vaccine supply in the United States [table S1 (1, 4, 5)] is largely a consequence of this view. Development and supply of vaccines that are needed primarily in the poorest countries is even more problematic,

which explains why no major pharmaceutical company has a large-scale vaccine development initiative for tuberculosis or malaria.

While industry finds vaccines unattractive, policy-makers complain that the cost is prohibitive (6). Indeed, physicians are frequently not fully reimbursed for the cost of childhood vaccines they administer. The situation has deteriorated to a point that the Institute of Medicine in the United States has suggested that outbreaks of vaccine-preventable diseases may occur as a result of declines in state and national coverage rates (6).

Economists have tried to calculate the benefits of vaccines beyond the relief from suffering or direct loss of life (7, 8). They concluded that vaccines are cost effective because their cost is lower than the cumulative costs of treatment, hospitalization, working days lost, etc. For instance, the measles, mumps, and rubella vaccine (MMR-V) saves \$16.34 in direct medical costs for every \$1 dollar spent, whereas the diphtheria, tetanus, and pertussis vaccine (DTP) saves \$6.21 for every \$1 spent (7). However, we believe that if policy-makers were to include in the calculation the appropriate factors for avoiding disease altogether (the "intangible" benefits of health), the value currently attributed to vaccines would be seen to underestimate their contribution by a factor between 10 and 100.

A recent example shows that under the appropriate circumstances intangible val-

ues are easy to include. In response to the bioterrorist attacks, the U.S. government mobilized large amounts of money, rushed to acquire the vaccines against anthrax and smallpox, and signed contracts to produce more of them (9), even though their safety profiles are inadequate by today's standards. Neither money nor technology was a problem. A budget of \$1.7 billion, more than the entire GAVI budget, has been suggested for "bioterrorism" research.

Governments have a number of tools to make vaccines more attractive to industry. One possibility for industrialized countries would be to offer tax credits; for example, to credit against tax up to 50% of qualifying R&D expenses would reduce significantly the cost of vaccine development and would provide an investment incentive. Although this benefit would be advantageous primarily to established companies that have profits, for others, the credits could be transferable and saleable.

Implementing regulatory and manufacturing reciprocity between the United States and the European Union would cut development costs by 20% or more and decrease time to market by at least 6 months. The increased revenues for early approval and the decreased costs may add up to several hundred million dollars, an amount almost equivalent to that needed to develop a new vaccine.

Public-sector agencies should cease using their large-volume purchasing power to command large discounts when buying vaccines. Recently, Wyeth Lederle Vaccines proposed a price of \$58 per dose for their pneumococcus vaccine. This was highly criticized by the CDC, which demanded a discount of more than \$10 per dose. If instead of a discount, the government had demanded reinvestment of \$10 per dose in research and development they could have paid for the development of a new vaccine within 2 to 3 years.

Extending patent-term for vaccines to exceed that permitted for other products under the Drug Price Competition and Patent Term Restoration Act of 1984 would also provide incentives to industry. Currently, patent extensions cannot exceed half of the development time up to a maximum of 5 years, and there is a total limit

of 14 years for a patent. Three years of additional patent extension could be worth several hundred million dollars.

Creative use of the orphan drug law could provide six additional months of marketing exclusivity on the product of choice to the industry that had developed an innovative vaccine. In other words, we propose that marketing exclusivity should be transferable to other products. For high-revenue products, such marketing exclusivity could be valued in the hundreds of millions of dollars.

It should also be possible to decrease liability risks, by means of government indemnification of damages caused by side effects from licensed products (assuming no negligence) and establishment of a regulatory compliance defense against tort suits for damages caused by vaccines (10). This would imply, in effect, that when a pharmaceutical manufacturer meets the regulatory requirements for vaccine approval, any mishap from use of the product would be considered to be wholly unforeseeable. The manufacturers' liability

would be mitigated by the extensive regulatory control of the FDA over their products from the earliest stages of clinical research to marketing approval, postmarket surveillance, and preparation of labeling and advertising materials. Additional incentives would include exemption from FDA user fees for vaccine-related regulatory submissions and health-care insurers' exemption of vaccination from plans in which the insured must pay "first dollar" health-care costs (which discourages the insured from opting for prophylactic, discretionary medical interventions). A healthy industry in developed countries will guarantee a steady development of new vaccines.

For developing countries, there have been several thoughtful economic proposals put forth for underwriting the costs of vaccine development and their subsequent purchase and delivery (11, 12); however, in our minds, the proposals go in the right direction but do not go far enough. They rely on charities and limited government funds without creating a self-sustaining system that could be achieved by simply attributing the correct economic value to vaccines. Difficulties

already encountered in the field have raised doubts about the long-term sustainability of the present GAVI plans (13).

How do we mobilize governments in developing countries to be proactive? One UN commission suggested that "rich" countries put aside 0.1% of their gross national product for health services for the world's poor (14). Perhaps governments should commit to a dedicated health insurance that is able to guarantee the recommended vaccines. If international treaties to limit nuclear devastation or land mines can be forged to prevent wholesale destruction, why can't we forge international agreements to save untold numbers of lives? Even the most recalcitrant of warlords have suspend their activities for a time to permit immunization (15). Tapping despair for one's lost children is a powerful tool to recruit new terrorists or to appeal to those who are discontent with their government. In fact, a relationship exists between childhood death rates from vaccine-preventable infections and the probability of a nation's becoming engaged in armed conflict (16). A long-term investment in health using available technology makes more sense than investment in an outmoded antimissile defense system based on unproven technology and of limited use against vague threats of bioterrorism. Or, perhaps more realistically, there needs to be room for both in enlightened societies.

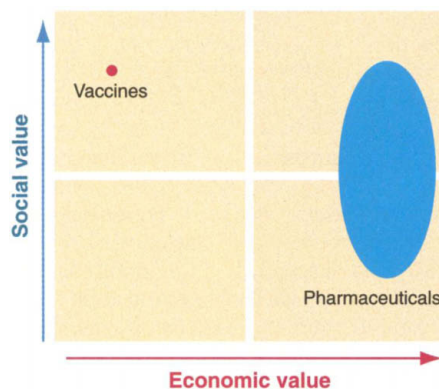


Fig. 2. Vaccines' value. Social versus economic value of vaccines.

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