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Review

Successes and failures: Worldwide vaccine development and application

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ABSTRACT

The impact that vaccines have had on world health has been great. The misery prevented and the lives saved have been impressive. But all has not been good. As one looks at the success, one can also see the missed opportunities. This discussion takes a broad, worldwide view of vaccines - from early research, through development and application. It examines our successes and our failures and looks with great optimism towards a future having great potential to prevent much of today's suffering from infectious diseases.

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Vaccines are such wonderful tools of medicine. Because of their use, the horrors of many diseases such as smallpox, diphtheria, tetanus, measles, diarrhea and meningitis, have, in many areas of the world, been relegated to the past. No doubt, the progress has been great and the misery prevented and the lives saved have been impressive. But all has not been good. As one looks at the success, one can also see the missed opportunities. This discussion will take a broad view of vaccines – from early research, through development and application. The focus, for obvious reasons, will be worldwide as these infectious diseases do not respect national borders and, as a result, vaccine developers and users must view the world as a single place where humans and animals interact in an environment full of potentially dangerous infectious agents.

The bio-technological advancements over the years have given us laboratory powers to understand disease etiology and produce newer and better vaccine products and newer and better ways to deliver them. The results have been astounding – including the total eradication of one of human-kinds most dreaded scourges – smallpox – and the prevention of a myriad of other dangerous infectious maladies. Indeed, the advancements in microbiological techniques, the better understanding of disease etiology, disease occurrence and the subsequent development of tools for their prevention, have been nothing short of revolutionary. These technical advancements, linked to the more recent increase in investments by foundations, governments and not-for-profit institutions in vaccine development and delivery, have been nothing short of phenomenal.

But it has not been easy. The process of vaccine development, from basic research to uncover disease etiology, through vaccine construction and pre-clinical and clinical testing, to actual application and disease control, is arduous. It is technically challenging, expensive and time consuming.

Yet the ultimate rewards are indeed great. Diseases of great morbidity and mortality one day can be all but forgotten the next. Again, take smallpox. It was a horrible disease. Dr. Edward Jenner's vaccine was based on the observation that ONLY the milkmaids of 1700 England had faces free from the pock marks of the disease. Instead, these milkmaids had pocks of their hands from previous infections from cowpox virus that protected them. Everyone else, from princes to paupers [1], had either died or was marked by the smallpox virus itself. Ultimately, the epidemiological understanding that humans were the only host for smallpox, combined with advances in vaccine manufacturing and delivery technologies, led to the global commitment to eliminate the disease. But such technology and commitments alone were not enough. The brilliant strategy of “search and containment”, brought forth by Foege, Millar and Lane in eastern Nigeria in the 1970s [2], allowed for the eventual elimination of that disease from the world.

Although smallpox is the only disease to have actually been eradicated, there are more that, through the application of vaccines, have seen marked reductions if not total eradication. The explosion of vaccine development in the last 50 years has seen diseases like polio being pushed into ever decreasing regions of the world. Others, like whooping cough are never seen in industrialized countries until unwise anti-vaccine movements bring the rates of vaccine coverage down enough to allow its return. And diphtheria, tetanus and yellow fever are seldom seen by most physicians

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outside of less developed countries (LDCs). More recently childhood meningitis and hepatitis A and hepatitis B are following the same path. Equally spectacularly, thanks to the ingenious and energetic pursuit of researchers, others like cervical cancer, will hopefully follow soon.

When added together, the contributions to world health from these remarkable products is nothing short of astounding. Whether considered in lives saved, health resources saved or person years of life saved, vaccines are some of the best investments that societies can make [3].

So that's the good news. Now let's look a little deeper and explore where, despite the overall good news, we can see where we missed the mark on some scores. First let's look not just at how much we have progressed but how long it has taken us to get there. Again, we can start with smallpox, a horrific disease that everyone at risk shuttered at the thought of. Early vaccination started in 1791 while vaccine became widely available by the early 1900s. Yet, it took decades longer to totally eliminate transmission in North America and Europe (between 1930 and 1950) and years more to eliminate it from the rest of the world (in 1977).

Polio, the second disease chosen to be eliminated has shown a similar pattern. Polio vaccine was first licensed in 1955 and was eliminated in the US and Europe after 36 years. Yet for the rest of the world, it persists in 2010, 55 years after the vaccine was licensed.

For both of these diseases, although safe and effective vaccines were available, they were not provided to many of those at risk and, as a direct result, immense numbers of cases and deaths occurred during these intervals. For example, at the time the World Health Assembly called for smallpox to be eradicated in 1967, an estimated 13,100,000 cases occurred annually in the 33 endemic countries [4].

Similar costly delays have occurred with essentially all vaccine-preventable diseases. Again let's take one of the oldest – the standard DPT vaccine used since the 1940s. Worldwide low coverage levels (<20%) existed until 1980 (Fig. 1) when international support was initiated. The result: by 1990, worldwide coverage reached 75%. Similarly, for hepatitis B there was initial slow worldwide delivery. This vaccine was first licensed in 1980.

Yet it took over 25 years to reach 65% of the population in adopter countries (Fig. 2).

For each of these vaccine-preventable diseases, the delay in delivering vaccine resulted in millions of suffering and dying children.

To fully understand the real costs and reasons for the delays of preventing these diseases, let's take a broader look at vaccines – from initial development to population-wide application. At the earliest stages, we need to fully understand all of the steps and costs involved in vaccine development.

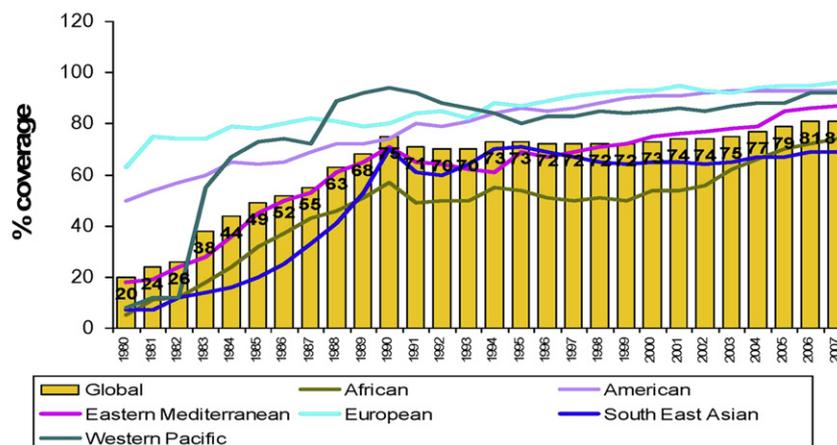
Note here that I use the term “development” – meaning those efforts which take place after the fundamental “research” has uncovered the cause of a specific disease. It is important to make the distinction here between the two activities (research and development) for each has very distinct output measures. In the 2001 World Bank Report on vaccines, McKinsey and Company described the distinct output differences between institutional basic science research and actual product development by industry: “The public sector institutions involved in vaccine R&D are primarily focused on basic science knowledge diffusion, rather than single-mindedly solving applied development problems to ensure large scale, consistent production. The incentives in the public sector reinforce this knowledge focus and are generally inconsistent with efficient production of commodities”.

In other words, the primary role of public sector academic research institutions is to focus on discovery and the outputs of their efforts are judged by the amount of knowledge they accumulate as measured by the number and value of the research manuscripts they publish in the scientific literature. On the other hand, the role of industries is the actual development and manufacture of products. Their output will be judged by the number of products (in this case, vaccines) they actually develop and deliver and, in the case of the private sector, the level of profits they receive from selling these products.

The lessons here are several. First, if societies want new vaccines they need to have and support both arms of this greater development process – the early academic “discovery” arm and the later, industrial “development” arm. Both are essential if societies are to have safe and

Global Immunization 1980-2007, DTP3 coverage global coverage at 81% in 2007

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Source: WHO/UNICEF coverage estimates, 1980-2007, as of August 2008
193 WHO Member States.



Fig. 1. WHO Region-specific immunization coverage with 3 doses of DPT between 1980 and 2007.

Number of countries introduced HepB vaccine* and global infant HepB3 coverage, 1989–2007

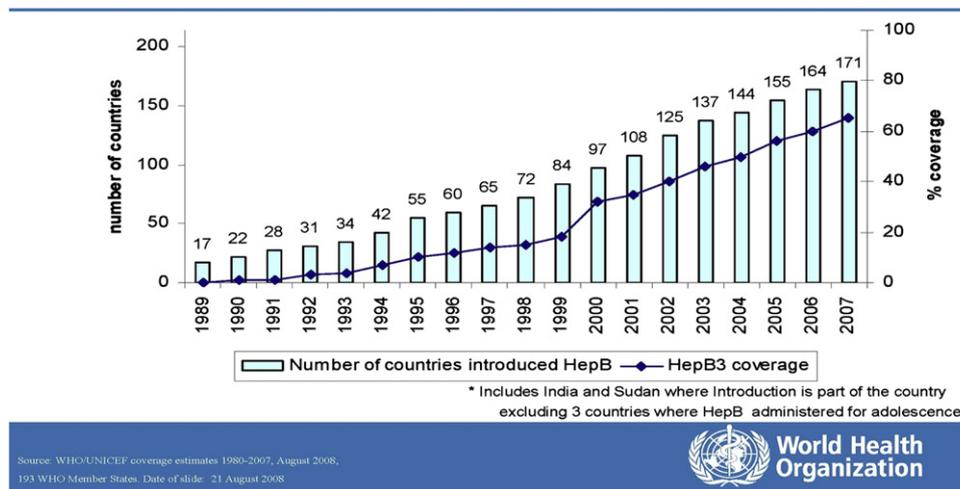


Fig. 2. Global hepatitis B vaccine. Number of countries introducing vaccine and percent of infants receiving 3 vaccine doses. 1989–2007.

effective vaccines. Second, all involved must understand the amount of time and money required to bring these vaccines from the bench to the people. Time can be measured directly. Cost data, on the other hand, are more difficult to obtain from industry. Such information is not readily available for most vaccines. Yet, recently, two companies have released some cost data that can be used as examples. One, VaxGen, reported on the costs of its failed HIV vaccine. They stated that their total costs, through phase III, were approximately \$300 million [5]. The other company, Aviron, reported the costs required to develop their Flumist nasal influenza vaccine. Those costs were estimated to be \$340 million for a fully licensed product [6]. For both of these products, the time from bench to end of phase III testing and/or licensure took a decade or more and we can be assured that by the time the final product would have reached the street, the costs would be two to three times higher.

Despite the limits of available information, we can certainly conclude that successful vaccine development takes a great deal of time and a great deal of money. What then spurs societies to make such an investment? In the end, it is social value. If the society values what they receive from vaccines and the prevention of disease that follows, they will continue to invest in future development. But this may be an oversimplification. In the real world, things are more complex. Fundamental in gaining an understanding of the complexity is seeing the difference between disease treatment and disease prevention. Everyone understands disease treatment – someone develops symptoms of a disease, is brought into the medical system to be diagnosed and given appropriate medical treatment. For prevention, a more subtle understanding is required, unless a raging disease epidemic is occurring in a population. Under normal conditions, people have to intellectually understand that there is a hidden risk of a given disease and that, with such a risk, they should ensure that all of their children receive vaccines to eliminate the risk. Furthermore, everyone must understand that, like the medical treatments they demand, vaccines cost money and someone, either our governments or ourselves, must come up with the money to pay for them.

Here is where the system, at least viewed from the vaccine industry perspective, has failed. Industry executives' major objective is to maximize the company's profits for their investors. Given that many of the technical skills required for successful preventive vaccine development and production can be applied equally well to

therapeutic medicinal development, these executives have a choice of investing their resources into a variety of development projects. To make such decisions from the plethora of projects presented to them, they will need to explore the likelihood of technical success of each project combined with an estimate of financial return should the project be successful. Here is where the influence of social value comes into play. Pharmaceutical executives are very aware that when citizens get sick, they or their relatives are often insistent that the best that medicine can offer should be delivered. In other words, people give curative medicine high priority.

In contrast, preventive medicine and the vaccines that are required for it, get much less interest. Preventative medicine is of the future while curative medicine is very much of the moment. And most governments, certainly elected ones influenced by individuals or organizations insisting on immediate cures, are very much focused on the short-term moment. Support for vaccine development and use depends on a mature and educated group of experts who review data and make recommendations for development and use. Unfortunately, such experts are often far removed from the political powers that ultimately make the financial decisions on which successful vaccine purchase and delivery depend.

Before the reader becomes irritated by the lack of interest in vaccines coming from commercial pharmaceutical/biotech companies, let's take a moment to sit in on a theoretical pharmaceutical company Board of Directors meeting. On that Board, members have the legal responsibility to protect the financial interests of their investors. At this Board meeting members are presented with two proposals for support of two multimillion dollar projects. One is for a vaccine for a worldwide disease for which the protective immune responses are not known. An exciting, very sharp investigator from the company presents a plan to understand the disease and make a vaccine for it. The second investigator makes a pitch for support for his cancer therapeutic product where, again, the etiology is unknown, but recent research has demonstrated the expression of a unique surface protein in 25% of cases against which the investigator has already produced several monoclonal antibodies (MAbs) that could bind to the cancer cells and potentially decrease the risk of death.

Let's assume the costs of each project are the same, approximately \$300 mm to market. After the scientists have left the Board meeting, the company's business person outlines the potential

profits from each of these proposed products. Bottom line, assuming equal probability of technical success, the anti-cancer MAbs can be priced very high (similar to other cancer therapeutics) with a very clear market in industrialized countries with very rapid use once licensed – even if the target protein is expressed in only 25% of cases. In contrast, for the vaccine, although very important and likely to do great good for large numbers of people, the speed of uptake will depend on an unknown private sector market together with an even less dependable public sector market. Decision made. Follow the therapeutic market and recommend the vaccine team re-direct its research to therapeutic agents.

The sad “bottom line” of this hypothetical, yet far too often “real”, scenario is that orders of magnitude increases in public good would likely be achieved by the opposite decision. Vaccines, over the years, have been extremely cost effective tools for both saving resources and preventing suffering and death. The problem here is not the pharmaceutical industry. They are doing what they should – following the “values” (what we will pay for) of the society. The problem is that today’s societies, given the political systems that guide them, have great difficulty acting where long-term benefits are often beyond the intellectual, political and business capacities of the system to deal with.

As a result of this “market failure”, in actuality a social failure, industry often sees valuable vaccines as being undervalued and not worth pursuing.

Why does “society” undervalue vaccines? Here the system seems remarkably failure prone. Wealthy people, especially in industrialized countries where most vaccine-preventable diseases occur at relatively low incidence, have little immediate incentive to immunize their children. Here the remarkable success of vaccines has, ironically, undercut the value given by these societies for vaccines. People in industrialized countries rarely have any experience with the horrors of these diseases. Only when over-protective parents refuse to vaccinate their children do these preventable diseases re-surface [7,8]. Less wealthy people in industrialized countries may, themselves, appreciate the value of vaccines more, but are dependent on chronically underfunded public health departments to deliver vaccines to their children.

But why are public health departments underfunded? Here we return to the previous discussion comparing the public’s interest in “preventative” versus “curative” medicine. When individuals, authorities or businesses are faced with hard decisions as to which of these they are going to fund, often the short-term curative medicine side wins. Although understandable from the emotion-of-the-moment decision process that is used, it makes very little sense from the full vantage point of long-term public good.

There is another culprit that comes into play here – cost-benefit and/or cost-effectiveness analysis. These analyses, especially for those of us involved in long-incubation communicable diseases, are especially irksome. To highlight the potential for misguided advice given by these analyses, let’s take a communicable agent that, after a long incubation period, is both communicable to others and, produces deadly disease in those infected. If this deadly disease takes 30 years post infection to develop (e.g. primary hepatocellular carcinoma following HBV infection), and a conservative discount rate of 5% per year is used, then, with this model, there is little or no predicted value of vaccinating to prevent the infection. Furthermore, as often occurs in this type of modeling, no added value is given to preventing subsequent infections that often come from being in contact with people suffering from these infections. There is often no realization that these slow progressors are, importantly, the source of infection for the next generation of cases. They ignore the fact that, if one could prevent the infection of the source, one would also prevent the next generations of cases in the future. If decision makers continue to ignore the nonsensical data that often

comes from such poorly conceived cost studies, we will never be able to appropriately prioritize the value of vaccines against agents having long incubation periods.

Now let’s narrow our focus from the whole world to just the less developed countries (LDCs). In these areas, the importance of vaccines in preventing disease can hardly be exaggerated. Whether judged by the number of people at risk of infectious diseases or the burden of vaccine preventable diseases, those living in less developed countries suffer the most (Fig. 3). Despite LDCs having this extraordinary burden of vaccine preventable diseases, the largest market, as defined by financial return from vaccine purchase, has been the industrialized countries. Fully 82% of the annual \$6 billion vaccine market comes from sales of vaccines in industrialized countries. In actuality, the public health benefit to the people of these wealthy countries has been quite remarkable. Indeed the resulting decrease or elimination of multiple terrible diseases has been a great accomplishment. And the return to the vaccine industry for their labors of several billions of dollars is something that should not be dismissed. Such returns should serve to hopefully re-energize the development of additional vaccines for diseases that continue to plague that part of the world.

Looking at this reality another way, however, we can see, as recently as 2001 (Fig. 4) that, although all vaccines taken together had a reasonable size market, that market (of all vaccines) was of the same size as the market for single drugs such as Lipitor® or Prilosec®. When compared to the equivalent sales in the less developed countries, the problem becomes more than apparent. Left to market forces alone, the people of less developed countries will suffer and die of easily preventable diseases. Although vaccines have great potential to prevent disease, they are expensive and time consuming to develop and companies that invest in this development will logically seek products that will give better returns on their investments in those countries that have financial resources to give such returns (Table 1).

To solve this problem, we have to use other forces than those of classic supply and demand. These other forces have been commonly referred as “push” and “pull”. That is, if the standard supply and demand forces do not stimulate important vaccines to be developed or used in LDCs, then resources have to be directed to either “push” new products through development with direct funding or, for those already in the market, “pulled” into use by direct purchasing of vaccines for delivery in LDCs. Through the years, there have been some remarkable successes for the push

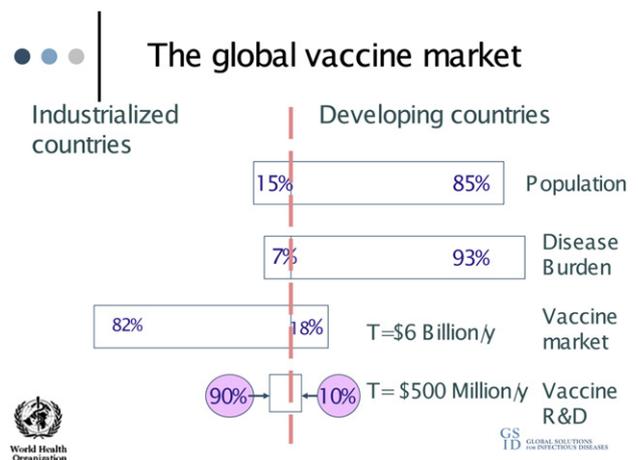
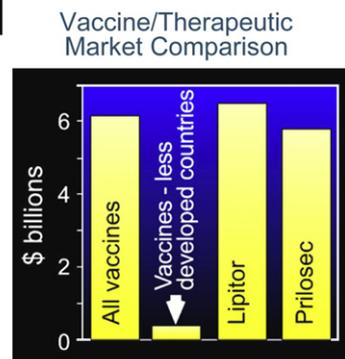


Fig. 3. The global vaccine market, global disease burden of vaccine preventable diseases and investment in vaccine research and development. Comparisons of industrialized and developing countries (Courtesy P. Whitehead).

Why Vaccines Fail to Compete



Note: Vaccine market data 2000, pharma sales 2001

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Fig. 4. Markets for vaccines and therapeutic drugs. Comparisons of world vs less-developed-country markets.

approach. For example, looking back a century or more, European research centers such as the Pasteur or Max Planck, made great progress in developing vaccines, many of which we use today. On the other side of the pond, the Rockefeller Foundation supported the development of the yellow fever vaccine and the Foundation for Infantile Paralysis/March of Dimes supported the development of both the killed and live polio vaccines.

After the polio vaccine in the 1950s, the model shifted somewhat with most vaccine development taking place in industry using their own resources. At that time, increasingly large amounts of basic research support was supplied by government science investments. Candidate products emerging from this early stage government supported research were then licensed to industry for further development. This approach, driven by profit incentives from industrialized country markets, had little effect on new products of value to LDCs entering the market.

Then, with the entry of the Bill and Melinda Gates Foundation (BMGF) in 1994, the field changed markedly. Furthermore, in 2006 when the large donations of the Gates family were augmented by donations from Warren Buffett, billions of dollars were brought into the LDC vaccine field. These donors joined with vaccine experts from around the world and caused a sea change in the world's ability to both develop and apply preventive vaccines for LDCs. With its focus on the world's poorest areas, the direct result of these efforts has been quite remarkable. In addition, the Foundation's ability to bring in other partners, both government and non-government, to share the immense financial burden of supporting the overall goal of immunizing the world's children has been nothing short of extraordinary in the history of vaccine development and delivery.

By examining both the financial investments for the delivery of existing vaccines to the world's poorest children and the investments in new vaccine development, we can gain some insight into the effect of these recent endeavors. For the former, take the

Table 1

Push: Public Private Partnerships in the Past.

Pasteur Institute	Diphtheria, TB, pertussis, tetanus
Rockefeller Foundation	Yellow fever
March of Dimes Foundation	Polio

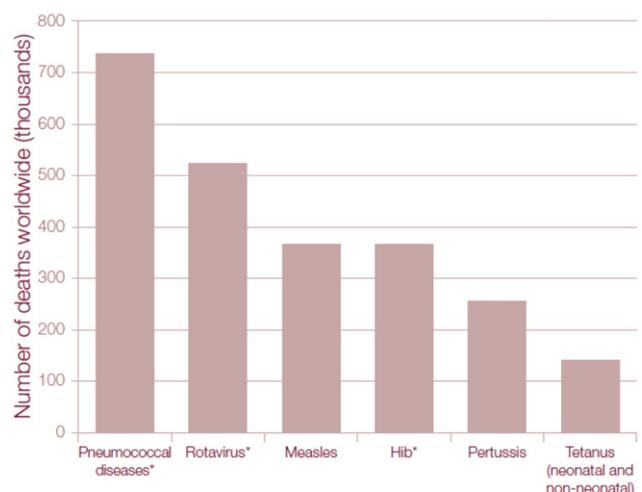
Foundation's remarkable initial investment that gave birth to the Global Alliance for Vaccines and Immunization (now GAVI Alliance). In 1999, the Foundation invested \$750 million US dollars as a start-up grant. By bringing in other contributors, between 2000 and 2015, \$3.7 billion US dollars have been committed.

Not surprisingly there have been substantial growth and management pains of GAVI, such as ongoing management challenges and the current estimates that vaccine demands will "bankrupt" GAVI in the near term. These well-founded criticisms, aside, few can avoid the overall sea change that has occurred by such activities in global immunization of children. For example, in less than 10 years, estimates are that GAVI-supported immunizations have averted 5,000,000 deaths of infants and children worldwide [9]. For hepatitis B virus vaccine alone, a vaccine which, as mentioned above, took decades to deliver widely even in the United States, over 192 million children have now been immunized around the world.

But the measures of success are not only in vaccine delivery. Vaccine manufacture has also been affected. By necessity, when any organization considers delivering vaccines to such huge numbers of children, the marginal costs of the vaccine make huge differences in the number of doses that can be afforded and, ultimately, delivered. With large tenders being offered, vaccine manufacturers around the world have scaled up to produce cost-reasonable, safe and effective products. Most notable is the recent entry of large manufacturers coming from emerging markets. GAVI reports that in recent years, over 40% of their vaccine purchases are now manufactured outside of the traditional US and European sphere.

But the veritable revolution in vaccines for LDC diseases has not been limited to vaccine purchase and supply. It has also had a profound effect on the development of new vaccines for diseases that affect people who live in these areas of the world. In response to this need, direct funding of new vaccine development has stimulated established vaccine companies to enter the arena of LDC vaccine development. In addition, new organizations and funding streams, supported by the BMGF and others, have emerged to drive vaccine development for specific diseases of less developed countries. Such drivers of development have taken various forms. Some

Leading causes of vaccine-preventable death in children under five years old, 2004



* WHO/Department of Immunization, Vaccines and Biologicals estimates based on Global Burden of Disease, 2004 estimates. Pneumococcal diseases and Hib estimates are for the year 2000.

Fig. 5. Estimated number of deaths in the world due to vaccine-preventable diseases in children under five years old in 2004.

have involved early research on which development is built. Others have established cooperative arrangements with industrial partners to accelerate development. Others have taken on the responsibility to speed access once vaccines are developed. For a review of these efforts, see the 3rd edition of “State of the world’s vaccine and immunization” [10] and the partial list.

Although this is a very exciting and ever-changing time for LDC vaccine development, looking ahead, one can visualize many challenges yet to be confronted. These challenges will be both structural and financial. One key element will be to continue to expand and perfect the capability of today’s vaccine delivery systems in LDCs. There is an urgent need to add the more recently developed vaccines, such as pneumococcal, rotavirus and Hib vaccines, to the LDC armamentarium. At the same time, we must realize that continuing high rates of disease that are preventable by older vaccines for measles, pertussis and tetanus, point to unacceptable weaknesses in our existing delivery programs (Fig. 5). Lessons learned from countries that have high rates of vaccine coverage need to be translated to areas where the success has not been so great. Then all areas need the resources, infrastructure and leadership to be enlarged to take on the new life-saving products that will continue to emerge from the development pipeline.

Another structural challenge involves the building of organizations that can guide the future development of vaccines for LDCs. With the skills of vaccine development primarily residing in the private sector, finding experienced people to join not-for-profits will continue to be a challenge. Moreover, many of the current organizations guiding LDC vaccine development are focused on a single disease and sometimes a single product. As new products move from earlier to later stages of development, different skills will be needed in these guiding institutions. Clearly, there will have to be a merging of product development responsibilities into larger organizations in order to keep talented people on board who can manage all stages of development.

From the financial side, fascinating challenges lie ahead. The challenges are fascinating in that one can see some very effective products moving down the vaccine development pathway. Such products will likely have immense potentials to prevent death and misery around the world. Yet, at least today, there are neither the financial resources to bring all of these products through development nor the purchase capacity to deliver them once developed. Here the entire field needs repeated doses of reality regarding the costs of both vaccine development and delivery. These incredibly cost-

effective products still cost hundreds of millions of dollars to develop. Yes, there are ways to do it more economically and these should be taken advantage of. Nevertheless, vaccine development is expensive and, in order to save lives and reduce the costs of disease, the world must be willing to put up the necessary resources to make it successful.

This is true both for the development of the new vaccines and their purchase once developed. One challenge, here, will be shifting more of the purchasing responsibility for older vaccines to national and local authorities rather than international organizations. The international organizations will be the only ones that can fund the actual development of new products. Yet it is unlikely that adequate funding will be available to simultaneously support both new product development and vaccine purchase at today’s level. On the other hand, national governments in some areas are now fully capable of purchasing some of the well tested, lower priced vaccines. Despite many of these purchases being funded by international organizations today, some of the costs will have to be taken over by national governments if newer vaccines are to be moved along the development pipeline.

All in all, the recent decades have been exciting. And the coming years, with all of the attention, progress and financial support coming to newer and better products and delivery systems, the field will continue to deliver more and better products that will markedly improve the health of the world’s children at very reasonable cost.

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