Global Alliance for Vaccines and Immunization: Financing Task Force

Issues Paper: Accelerating New Vaccines[1]

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Note: The authors are grateful to Ken Bernard, Scott Boule, Lance Gordon, Jim Jones, William Jack, Steve Landry, Orin Levine, Violaine Mitchell, Richard Mahoney, Julie Milstien, Bo Stenson, Philip Russell, Bob Snyder, Walter Vandersmissen, and Roy Widdus for extensive comments.

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Part

1

Cause for Action

R&D for "Near Term" Vaccines

Purpose of the Paper

This paper is about the magnitude of and reasons for global under-investment in research and development for vaccines that have the greatest potential health benefits for the developing world. It discusses the advantages and disadvantages of strategies to stimulate greater supply of vaccine products for poor countries.

The paper grows out of the work of the Financing Task Force (FTF) of the Global Alliance for Vaccines and Immunization (GAVI), which is charged with providing guidance to the global community on feasible, effective financing strategies to accelerate the development, purchase and use of priority vaccines[2] in developing countries. Specifically, it is a background document for the "Out of the Box" group, a working group comprised of experts in private and public finance, the pharmaceutical industry, and the health sector in developing countries that will meet in the summer of 2001 to debate alternative approaches to stimulating R&D and investments in expanded production capacity, and scale-up.

Organization of the Paper

The paper is divided into three sections, as follows. In Part 1, we highlight prominent symptoms of the imperfections in the vaccine market, describe the reasons for under-investment in R&D and manufacturing capacity, and seek to indicate the relative impact of each of these causes. We also highlight the potential benefits of public-private partnerships to address the problem, and identify the technical and other constraints that must be considered. In Part 2, we discuss in detail the advantages and disadvantages of "push" and "pull" strategies. In Part 3, we draw a set of specific conclusions about the promising next steps, and set out an agenda of questions to be addressed by the "Out of the Box" group (see member list in Annex 2). Basic information about GAVI and the role of the FTF is provided in Annex 1A-1B.

The Troubled Vaccine Market[3]

For the children of the developing world, there is an ever-widening gap between how much is *known* about preventing disease and how much is *done*. Despite unprecedented advances in understanding of communicable disease, and in the ability to interrupt

[2] meningococcal A conjugate, pneumococcal conjugate, quadra- or penta-valent DTP-based combinations, and rotavirus.

transmission, a great number of the world's children remain vulnerable. In this section, we present some basic facts about symptoms of dysfunction in the creation, production and uptake of new vaccine products.

The most important diseases among children in the developing world can be prevented with current or near-future vaccine technology. Within the developing world 20% of deaths of children under 5 years are attributed to acute respiratory infection, including pneumonia and influenza. Diarrheal diseases, including those caused by rotavirus, account for another 20% of deaths[4]. Measles alone caused 800,000 deaths in 1999[5]. Malaria, tuberculosis and HIV/AIDS also represent significant causes of mortality and morbidity among children. In total, three million children die each year from vaccine preventable diseases.

The potential market for vaccines in developing countries is very large. Annually, 64 million infants are born in low-income countries, and another 48 million are born in middle-income countries. Over the next 10 years, it is projected that the size of the birth cohort for low and middle income countries will increase by approximately 133 million[6]. However, the size of the market is measured not by the number of doses demanded or desired, but by the willingness to pay for those doses.

Experience delivering routine and newer childhood vaccines through the National Immunization Program has shown that immunization is highly cost-effective and cost-saving for health systems in the developing world. It is estimated, for instance, that the actual cost-effectiveness of hepatitis B vaccines would be $11-15 per life saved in low-income countries, currently not vaccinating against Hep B[7]. However, direct cost-savings are not the only benefit of immunizations. The indirect cost-savings realized are not insignificant. Pneumococcal disease provides a good example of why. When vaccines are not available, the disease is often treated with drugs. However, resistance to drugs is rising, rendering the treatments ineffective, and driving the costs of supportive care up. Meningitis provides another excellent example of why immunization makes economic sense. While a vaccine can prevent the infection and disease, drugs can only stop the progression of meningococcal disease, they can not cure the disease. However, most of the first symptoms of meningococcal disease are the result of permanent damage so by the time a patient comes under a doctor's care damage is already done. Permanent sequelae of meningococcal meningitis include hearing loss, vision loss, paralysis and mental retardation. The indirect costs of meningococcal infection (or Hib) continue to accumulate through out life – including supportive care and lost productivity Treating the epidemics is also expensive. When vaccination rates are low, epidemics which cause great disruption to both families and health systems result. Reacting to epidemics is not nearly so cost-effective as proactively working to prevent them.

Positive effects of vaccine introduction can be seen very easily. As shown in Figure 1, below, following the introduction of Hib vaccine in Uruguay and Chile, incidence of the disease dropped markedly.

[4] NIH data.
[5] WHO data.
[6] World Bank data.
[7] Miller, Mark A, and W. Dana Flanders. "A Model to Estimate the Probability of Hepatitis B- and Haemophilus Influenzae Type B-Streptococcus Pneumonia-Conjugate and Rotavirus Vaccines in National Immunization Schedules." *Health Economics* 9: (2000): 19-35.

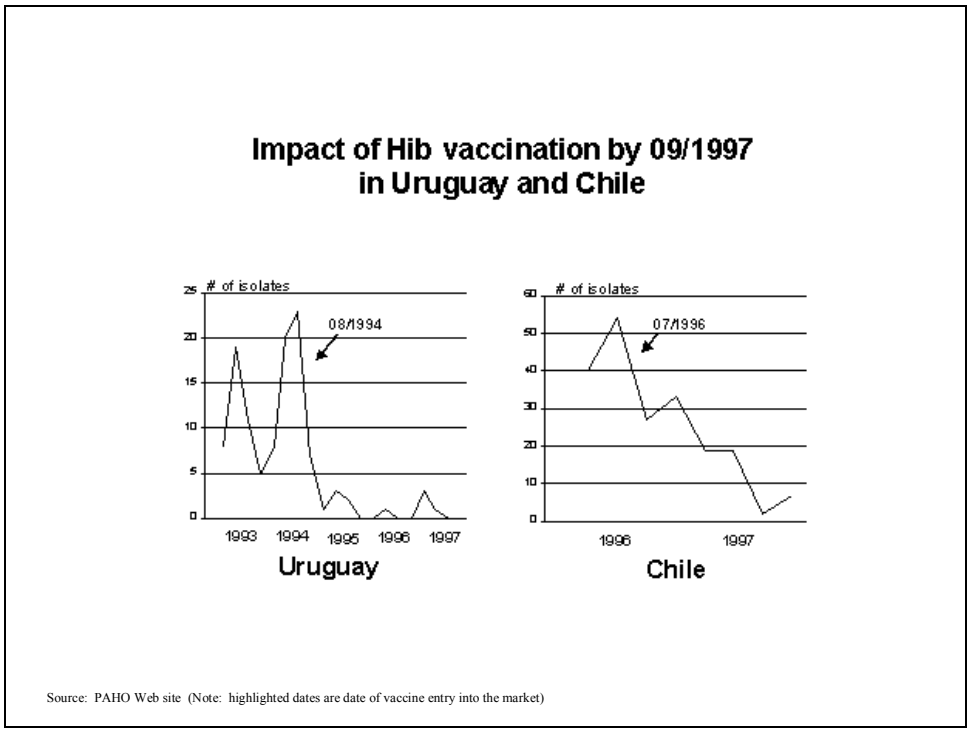


Figure 1: Impact of Hib Vaccine

A lapse which occurred in the treatment of measles in Macedonia offers more powerful testimony to the value of immunization.

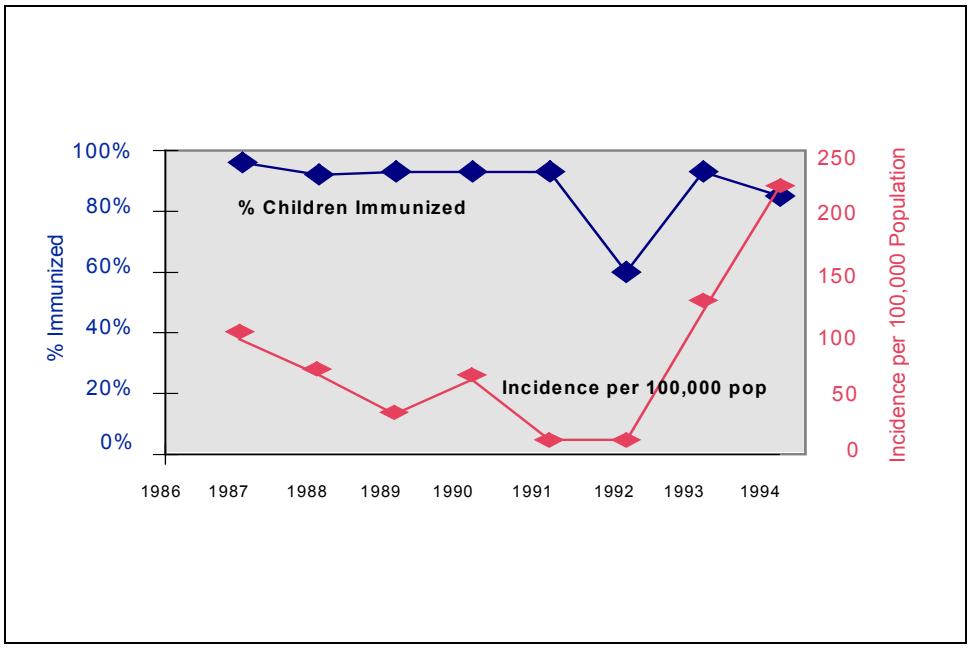


Figure 2: Immunization Coverage and Incidence of Measles: Macedonia (Former Yugoslav Republic): 1987-1994.

The benefits of vaccines extend beyond the immunized child, her community and the country in which she lives. Immunization can virtually eliminate the risk that the vaccinated child will become infected and, at relatively high levels of coverage, can greatly reduce the risk of transmission even to unvaccinated children. In global terms, recognizing that diseases do not respect borders, reducing the incidence of vaccine-preventable diseases in developing countries can have sizeable benefits for the industrialized world. In the case of polio eradication, for example, Taylor *et al* demonstrated that the benefits for wealthier countries outweigh those for the developing world[8]. The problem is that vaccines cannot be demonstrated to benefit the individual; their benefit is measurable only at the population level. In plain terms, if our neighbors are vaccinated they cannot spread infection to us. However, the difficulty of personalizing this enormous population benefit means that vaccines and vaccination programs are often under-valued. Not surprisingly, under-investment relative to the potential social benefits of vaccines has often been the result. This partly explains underproduction of immunization services.

Despite the indisputable benefits of new vaccines, and the potentially huge supply of product needed, the vaccines enterprise is characterized by low levels of investment in R&D. With some exceptions, the large multinational firms have not made investments in vaccine development that are equal to the magnitude of the problem. In 1992, only 4 percent of the US$55.8 billion spent on global R&D went toward disorders that account for most of the disease burden in the low- and middle-income

[8] Taylor, CE, Cutts, FT, and ME Taylor. "Ethical Dilemmas in Current Planning for Polio Eradication." *American Journal of Public Health* 87 (6): 922-925, 1997.

countries[9]. The situation had not changed much by 2000, when 10 percent of global research funds were dedicated to the 90 percent of disease burden that affects the world's poorest people. While it is true that much of the investment in R&D for industrialized countries furthers platform technologies that will benefit the development of many vaccines, R&D dedicated to the developing world needs remains low. Looking only at pharmaceutical investment specific to the developing world, a 1999 study found that only 1 percent of drugs to reach market between 1975 and 1997 were approved specifically for developing country diseases[10].

Capacity for production of vaccines that have a market in developing countries is also low (and in some cases diminishing). Industrial market producers seem to be moving away from the production of what are typically low-margin vaccines, or vaccines that are used mainly in the developing world. For example, the number of licensed manufacturers of yellow fever vaccine has declined markedly in the past few years.

The number of industrial market manufacturers supplying the low margin vaccines used in industrialized countries is also declining. The United States offers an extreme example of this phenomenon, as from the 1970's to today, the number of FDA licensed vaccine manufacturers to the United States Centers for Disease Control and Prevention (CDC) has dropped alarmingly (see Figure 3 below). The trend is true of global manufacturers as well. In the past few months alone, one major US manufacturer has announced that it will discontinue producing diphtheria and tetanus toxoids. Additionally, the pneumococcal conjugate vaccine programs of two other manufacturers are now in question. While new players are emerging to fill these voids, they have not replaced the multinational manufacturers, in some cases contributing to recent vaccine shortages.

[9] Kettler, Dr. Hannah E. "Narrowing the Gap Between Provision and Need for Medicines in Developing Countries," London: Office of Health Economics, February 2000.

[10] Pecoul, B., Chirac , P., Trouiller, P., and J. Pinel. « Access to Essential Drugs in Poor Countries : A Lost Battle ? » *Journal of the American Medical Association*, Vol. 281 No.4, January, 1999: pg 361-367.

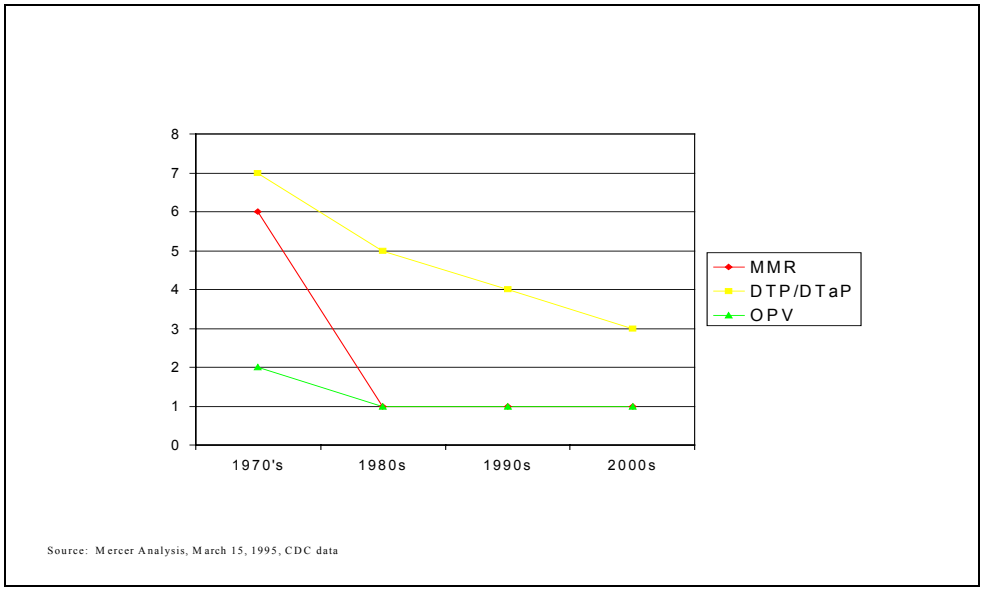


Figure 3: FDA Licensed Vaccine Manufacturers to the CDC

Finally, some of the essential childhood vaccines used by the US public sector are provided by off-shore manufacturers. For example, DTP/DTPa is provided by Aventis Pasteur, and GlaxoSmithKline, while E-IPV (inactivated polio vaccine) is provided in the US by only one manufacturer, Aventis Pasteur.

On the demand side, uptake of vaccines in developing countries has been slow, leading to a perception that the market is weak and uncertain. In part due to financing constraints, developing countries have been relatively slow to introduce newer vaccines, such as Hib and Hep B, into their vaccination schedules. While uptake varies by country, the overall rates of uptake for developing countries have been disappointing.

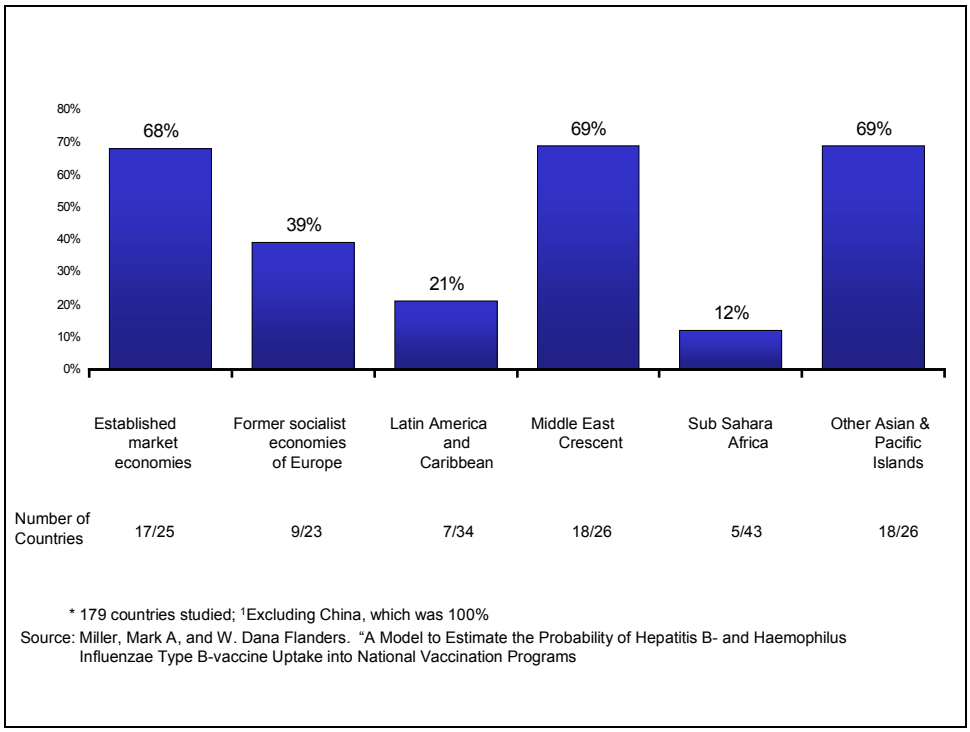


Figure 4: Different Regions have Different Rates of Vaccine Uptake: Frequency of Adoption of HB into routine vaccination schedules, October 1998. Percent of nations.

Understanding Low Investment in R&D and Manufacturing Capacity

The private sector invests relatively little in R&D and manufacturing capacity for vaccines that would benefit developing countries for five basic (and closely linked) reasons: competing uses for resources are more profitable; demand for new products is perceived to be low; costs of production are relatively high; market pressures are intense and rapidly changing; and products for the industrialized world are diverging from those for poorer countries.

Pharmaceuticals for wealthy countries offer a larger market than vaccines for poor countries. The global vaccine market of US$5.4 billion represents a fraction of the US$337.2 billion pharmaceutical market[11]. Furthermore, of global pharmaceutical expenditures, low and middle income countries account for at most 18 percent of the total. Vaccines account for a miniscule portion of that 18%, making investing in them a sometimes unattractive option[12].

[11] IMS Health Data, and McKinsey study, May, 2001.
[12] "Creating Global Markets for Neglected Drugs and Vaccines: A Challenge for Public-Private Partnership." Global Health Forum I: Consensus Statement, February 2000.

Box 1. Drugs vs. Vaccines

The differences between drugs and vaccines fall into three major categories: market, product development and production, and product use, with market-related differences being the most pronounced and significant. First, vaccines are a preventive intervention, as opposed to drugs which are curative. Private individuals are much more willing to pay "whatever it takes" for curative drugs, while the public sector is often the funder of preventive vaccines. Stated simply, the likelihood that people who are sick will pay high prices for drugs is typically higher than the likelihood that healthy people will opt for or pay for preventive vaccines The implications of this public-private, preventive-curative split may be seen in the value of the each market. At US $5.4 billion dollars, the vaccine market represents just slightly more than 1.5% of the US$337 billion drug market.

From a production and product development standpoint, the differences continue. The quality control and regulations for vaccines are much tighter than for drugs, driving costs up. However, scale effects in vaccines have historically tended to be more significant than in drugs, which brings costs down.

The differences in use are also important to note. Vaccines are used in all healthy children, and therefore must be nearly 100% risk free, as opposed to drugs which are used primarily for sick people, who may be more willing to tolerate side-effects. This difference increases the accountability, and therefore the risk for manufacturers of vaccines. With vaccines, individual benefit cannot generally be demonstrated while side effects are easily demonstrable, a dynamic that has generated prohibitive product liability burdens. In 1985 there were over $4 billion product liability suits against DTP vaccine in the U.S.

Limited financial capacity and the public sector's slow adoption of new vaccines signal low effective demand. Manufacturers doubt that the public sector in developing countries will be able to mobilize sufficient resources to purchase new vaccines, which will likely be priced significantly higher than the current "pennies per dose" routine childhood vaccines. Although demand for vaccines may exist on the part of people who desire them, manufacturers' projections of demand are based on the money available to purchase vaccine. Past and current uptake is a major factor from which the future demand potential of vaccines is extrapolated. A historical pattern of slow uptake of new products combined with demand for extremely low pricing makes industry skeptical that the demonstrated demand in the developing world is backed by dollars.

Production costs have been rising. Production costs have risen in the past 10 years for three reasons: First, more stringent regulation has boosted production costs. Second, new techniques including complex conjugation procedures, purification, and aseptic filling without preservative, require expensive equipment and significantly add to the difficulty and cost of production, while also reducing the potential for economies of scale. Third, the ban on thimerosal, a mercury-based preservative, in the United States, has forced manufacturers supplying the US market to move to more expensive single-dose vials. Pharmaceutical companies assert that their increases in price are due to these rising production costs.

Manufacturers most likely to invest in R&D face increasing market pressure from manufacturers that focus primarily on production. Two simultaneous trends have been identified. First, the number of manufacturers of essential

vaccines has grown in the past twenty years. However, virtually all of that growth has occurred among smaller manufacturers headquartered in middle- and low-income countries. Secondly, the number of industrialized-country based manufacturers who produce vaccines for the developing world has dropped. This drop is the result of both consolidations, and of multinational manufacturers exiting the market for developing country vaccines. In the U.S., for example, the number of vaccine manufacturers supplying the CDC National Immunization Program over the past 20 years dropped from 15 to 8 (inclusive of licensed manufacturers of MMR, DTP, OPV/E-IPV, DT, Hep B.)

Less money is available for R&D on vaccines for developing countries The industry consolidation among suppliers to wealthier countries—combined with the rise of developing country vaccine manufacturers with products on the WHO pre-approved list to supply UN vaccines (see Box 2)—has had sweeping implications for both the quantity and type of R&D. In the past, for example, each of the seven or eight leading manufacturers would be working on five to six vaccine-related R&D projects. Today, with the industry consolidated to four major multinational manufacturers, the number of R&D projects undertaken by global pharmaceutical firms has dropped accordingly. Smaller and emerging manufacturers are less likely—and financially less able—to take on the risks of product development. For the development of major new vaccines, the world still looks to the large, multinational manufacturers—and those manufacturers are already seeing to see the future market as being the wealthier countries of the world.

Box 2. Changing Dynamics of the Pharmaceutical Market in Developing Countries

The increasing numbers of parastatal industries and private manufacturers in middle income and developing countries noted above is providing a serious challenge to the pharmaceutical industry. While small numbers of these firms have long been in existence, it is only in recent months that a large enough group has been successful and vocal enough to garner public attention. These two types of companies have lately shown a willingness to enter the market with lower prices for drugs, achieved either by copying drugs made by larger companies (allegedly infringing on international patent rights [IPRs]). In February, 2001, Cipla Ltd., of Bombay, a major manufacturer of generic drugs, offered to supply as many doses as requested of triple-therapy drug "cocktails" at $350 a dose to Doctors Without Borders. The normal price of the AIDS cocktail in the West is $10,000-$15,000. The Cipla "cocktail" is made up of drugs for which pharmaceutical companies hold the patent. At the point of this writing, the patent holders had not yet commented on what they would do if Cipla sold the drugs on the open market[13]. The emergence of these middle-income and parastatal players willing to supply lower priced generic drugs is having a substantial impact on the pharmaceutical industry. Three large pharmaceutical companies: Merck & Co., Bristol-Myers Squibb, and Abbott Laboratories, have all recently announced that they will cut the prices of their HIV drugs in response to public pressure, pressure from African nations, members of the international community, and AIDS activists objecting to the high prices for HIV drugs[14]. Some members of the international community worry privately, however, that multinational corporations may withdraw altogether from their commitment to supply marginal developing country markets, thereby exacerbating an already fragile situation.

Products for wealthy and poor countries are diverging. A threefold shift has occurred: from "global" to regional products, from one type of vaccine for one disease, to many types of vaccines for the same disease, and finally from equal numbers of vaccines

[13] McNeil, Donald G. Jr. "Indian Company Offers to Supply AIDS Drugs at Low Cost in Africa." *New York Times* February 7, 2001, A1.
[14] "Abbott Slashes AIDS Drug Prices in Africa." USATODAY.com March 27, 2001.

for different regions to a large disparity in number of products delivered to developing vs. industrialized countries. First, different diseases are being treated in different parts of the world. For instance, yellow fever vaccine is needed in Africa, but only for the travelers' market in industrialized markets. In the second trend, different vaccines for the same disease are now available for different markets. In the past, the typical model was that vaccines moved sequentially from developed to developing countries over a period of time. However, today, the same diseases are being targeted through different vaccines, depending on geography and cost. For example, in the 1990s some industrialized country markets adopted DTaP as the vaccine of choice over DTwP. Although more expensive and some believe perhaps not quite as efficacious as DTwP, DTaP vaccine has fewer non-serious adverse events associated with it and has enjoyed a greater acceptance among parents in industrialized countries. Finally, in the third trend, as the number of vaccines used in industrialized countries has increased from 7 to 12, the number of vaccines used in developing countries has only grown from 5 to 7.

Baseline	Tailored to the DC Market	Tailored to the Industrial Market
Measles	Measles	MMR
DTP	DTwP	DTaP
OPV	OPV	IPV
TT	TT (Td in some areas)	Td
Hep B	Monovalent, DTwP-Hep B	Monovalent, DTaP-Hep B, DTaP-Hep B-IPV-Hib, Hep B-Hib, Hep A-Hep B
Hib	Monovalent, DTwP-Hib, DTwP-Hep B-Hib	Monovalent, DTaP-HepB-IPV-Hib, Hep B-Hib
Mening A/C polysaccharide	Meningitis A/C conjug (wanted)	Meningitis C conjugate, (Meningitis BC conjugate)
Pneumo polysaccharide	11-valent conjugate-wanted	7-valent conjugate; 11-valent under development
Product presentations	Multidose, thimerosal	Single dose, no thimerosal

Figure 5: Products are being Tailored to Different Markets

The divergence in the number and type of vaccines, as well as the supplier is generated in part by the investment choices of the four largest vaccine manufacturers. As the industry has consolidated, R&D budgets have shrunk, and competition for capacity has become fierce, some large pharmaceutical companies are making a tradeoff which favors global or industrial market products which have higher margins than those products tailored to developing countries. The shifting focus of the multinational firms is creating a niche in developing country vaccines with higher production costs, or lower potential profitability. Manufacturers who are willing, for instance, to produce a product for Unicef that requires lyophilization (a freeze-drying procedure which is costly, and ties-up machines which could possibly be more profitable used elsewhere) are experiencing better uptake.

Box 3. The Domestic Production Option

One potential option often put forth is to use domestic producers in developing countries. Proponents of domestic production have argued that it is more cost-effective and more sustainable, and that difficulties with foreign currency exchange are avoided. Domestic production, while improving, is not a viable option for many of these necessary vaccines. Historically, most local producers are driven by two main factors: "a sense of obligation to meet public health duty and provide vaccines to its citizens," and "the [perceived] ability to control better the reliability and source of vaccine supply." However, a 1999 CVI task force found three major drawbacks to local production.

- Local vaccine production may be exempt from the National Regulatory Authority, and thus is often poorly regulated or controlled. Vaccines are therefore of inconsistent quality or cannot always be manufactured in reliable quantities.

- Local vaccine production is usually not less expensive than importing vaccines, as was previously assumed, for two main reasons. First, because vaccines are capital intensive, cheap domestic labor does not provide the comparative advantage that was previously assumed. The second reason often provided for why domestic production was more cost-effective was that it avoided costly foreign exchanges. However, vaccine production demands specific inputs that are often not available domestically, and must be imported, thus encountering the same foreign exchange problems that domestic production was thought to avoid

- The long-term stability and viability of vaccine production facilities requires unwavering political commitment and a strong management infrastructure that responds well to change. Historically, however, domestic production facilities have been run as public sector bodies, even though the demands of vaccine production exceed the level of support traditionally provided to public sector bodies.

These findings indicate that while local production remains an important option for some developing countries, it is far from the optimal solution for most[15].

A Sense of Urgency, a Call to Action

Although not new, the problem of under-investment in R&D for vaccines against developing country diseases recently has recently received much more attention. In the past year, communicable diseases and the drugs and vaccines to prevent and cure them have been prominently discussed. Governments, non-government organizations (NGOs), and the general public have all dramatically increased their focus on these issues.

Leaders of the industrialized world have taken on this challenge. At the July, 2000 meeting in Okinawa, the G8 committed themselves to supporting significant improvements in health outcomes among poor countries. Specifically, the G8 pledged to reduce the number of young people infected by HIV by 25%, and the number of

[15] Brewer Katie, and Diana Chang Blanc. "Issue Paper: Motivations for Local Vaccine Production." Children's Vaccine Initiative, 1999.

tuberculosis deaths by 50% over the next ten years. Following the G8 declaration, on October 19, 2000, the U.K.'s Secretary of State, Clare Short added strong support, by issuing a public call for increased resources for new drugs and vaccines for the diseases which affect the poorest people in the world. Her comments also noted the need to create environments in which partnerships between the public and private health sectors can flourish.

Leaders of industry The declaration of the G8, and the significant involvement of the U.K. are just two highly visible symbols of the new (or newly recognized) interest in, and commitment to public-private partnerships. Industry too has acknowledged the need for creative solutions and partnership. In 1998 a "Round Table" between WHO and the pharmaceutical Industry was initiated by Dr. Gro Harlem Brundtland, the Director-General of WHO. The "Round Table" participants have identified several specific areas of interest for further collaboration.

Non-governmental Organizations [NGO] contributions NGOs have, for many years, played a critically important role in the delivery of essential health services in developing countries, working closely with international agencies, local communities and governments, and private pharmaceutical firms. In recent years, however, as the full force of the AIDS epidemic is being felt in Africa, some NGOs have become increasingly frustrated with the high prices charged for needed anti-retroviral drugs and have mounted general public pressure against multinational pharmaceutical firms. Having focused almost exclusively to date on efforts to force multinational companies to slash prices of AIDS drugs, some NGOs are now seeking to play a larger role in international initiatives to determine how public funds can be used to spur vaccine R&D and how these monies will translate into accessible and affordable drugs and vaccines for the developing world. It will be critical to engage the NGOs in discussions around the complex issues in vaccine R&D and production.

These specific examples represent a small portion of the vast number of academic papers, discussions, and declarations on the need for creative financing mechanisms and public-private partnership, which have become increasingly frequent in the last two years.

Funds and international collaboration are found in GAVI. The willingness to put money behind the talk about public-private partnerships has been evident in the contributions of donor organizations, most notably the Gates Foundation. Gates' gift of $750 million dollars to GAVI and the Vaccine Fund "put vaccines back on the world's agenda" and was followed by gifts from nations like Britain, Norway, the Netherlands, and the United States[16]. (The Vaccine Fund is the financial arm set up to support GAVI's initiatives.) GAVI's membership is made up of public and private sector leaders committed to real and long-term progress in immunization. The commitment of all members, combined with the streamlined structure of the GAVI Secretariat, means that GAVI has the ability to act more quickly than most partnerships or initiatives in the public domain. Furthermore, with the establishment of the Vaccine Fund, GAVI has real money to back up its ideas. With all partners working together with high levels of coordination, and money available to use, GAVI has the power to significantly alter investment and purchase patterns. The time to move from rhetoric to action has arrived.

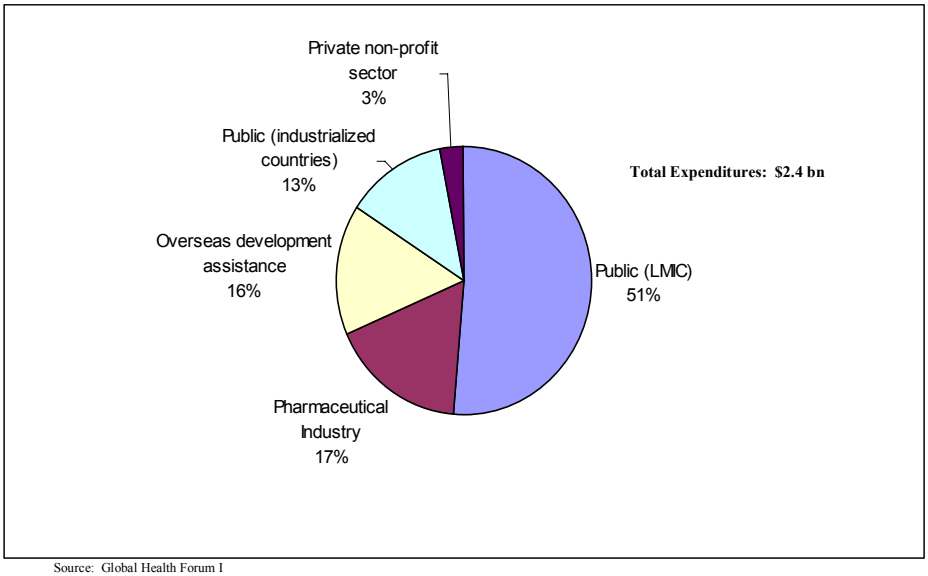
[16] Paulson, Tom. "GAVI's goal is clear, even if route to it is not." *Seattle Post-Intelligencer* (Seattle P-I.com) March 23, 2001.

The Promise of Public-Private Partnership

Accelerating the development, scale up and use of priority vaccines will require hard work from both the public sector and the private sector. Neither has the skills or expertise to solve these problems alone, each needing what the other side can offer. The public sector is particularly important in laying the foundation in basic research and setting policy. The private firms are skilled at driving the sciences toward a commercially viable product.

The public sector can mobilize funds and foster an environment conducive to research. The public sector's strengths lie in its ability to amass and coordinate large amounts of capital, a history of broad-based support for basic research, and in programmatic and policy experience at the country level.

The public sector has historically invested enormous resources in broad-based research, knowledge about a disease, its pathology, and its basis of immunity. The resulting findings create a foundation for product design, and systems for product development and evaluation.



Source: Global Health Forum I

Figure 6: R&D expenditures, 1992

The public sector also often can help with research and information on animal models, reagents, tools for the determination of disease, and epidemiology. Once the process is moved beyond initial and basic research, the public sector can help the private sector focus its applied research and design trials so that investments are maximized. At the country level, the public sector has extensive experience in working with local government, and can encourage local government to support or facilitate clinical trials. At times the public sector may be able to help influence, or even create, policy in areas where the private sector has limited leverage. In some cases, the public sector may also be able to help accelerate the introduction of vaccines into new markets where the private

sector does not have good access. Although this is not always the case, and there have been instances in which the private sector has been disappointed in the outcome of these efforts (e.g. Hib), this is a potential strength of the public sector. Finally, the private sector can benefit from the positive public relations that sometimes results from working with the public sector.

The private sector can mobilize the talent, and produce results. The private sector has a wealth of specialized expertise and knowledge that it brings to developing, scaling up, and producing vaccines. Good knowledge of manufacturing considerations, of costs, timing, and the technical issues of vaccine development and production is found with private firms. Industry brings a product-oriented, bottom-line approach, which is focused on "getting things out the door" as efficiently as possible. Finally, the private sector brings the capacity for efficient and reliable production on an ongoing basis.

Constraints to Rapid Increases in Investment in R&D through Public-Private Partnership

Despite the benefits of stimulating R&D for vaccines that would benefit the children of the developing world—and an international consensus may be emerging to do so—there are clear constraints that must be taken into account. Some of these constraints are tangible; others are attitudinal. Often the constraints are simplified into attacks on industry; however, the issues are real and must be addressed constructively.

The scientific feasibility of developing vaccines for certain diseases is questionable. For some high-priority diseases, the dearth of information on the pathogenesis of the disease is a limiting factor in developing a vaccine. Vaccines for parasitic diseases, like malaria, are particularly difficult to develop, as it is difficult to determine which portion of the lifecycle to target. In other cases, a lack of good animal models, or correlates of immunity for certain diseases, like HIV/AIDS, is a serious hindrance towards developing a workable vaccine.

Building up production capacity takes time, and occurs only when manufacturers perceive relatively low risk. For manufacturers, physical limitations represent major challenges to be overcome in order to produce vaccines. Regulatory issues are the major obstacle, necessitating serious time commitments and capital investments at nearly every stage of production. Due to their complexity and size, manufacturing facilities require large and early investment. Manufacturers must therefore allocate money years before a vaccine is projected to enter the market, and often before data showing the effectiveness of the product is available. At times they must make capacity investment decisions before major considerations like a vaccine's potential market are assured, or even before its efficacy and safety are established to a level sufficient for licensure.

Once a manufacturing facility is built, its capacity becomes relatively fixed. It is difficult to quickly scale-up production of an existing vaccine, and even more difficult to totally change the focus of a facility, as changes to the production process must be validated. Scaling up a filling line alone, for instance, can take two to four years.

Changing manufacturing facilities requires validation and regulatory approval, both of which are costly and time-consuming. The time, energy and money required to comply with regulations reduce the incentives to make these kind of changes, or even invest in vaccines to begin with. Whether a manufacturer wants to scale up a product, change the mix of an existing product, or introduce a new product in an existing facility large capital investment and extensive re-licensing are both necessary Furthermore, to introduce a product into multiple countries, the manufacturers must obtain licenses for each country which can also take years and much money. However, it should be noted that in least developed countries, governments sometimes use WHO pre-qualification as a favorable indicator to speed rapid national registration.

Distribution and infrastructure weaknesses hinder access to vaccines. Improving immunization infrastructure and distribution is a GAVI priority. In many parts of the world even though vaccines are given away for free they do not reach those who need them because of distribution and infrastructure weaknesses. Significant investments are needed in transport (revitalizing/extending the cold chain), storage, education and training[17]. Some public sector representatives have argued that access is secondary to the issue of whether or not a country decides to adopt a specific vaccine. They contend that the difference between a 50% and an 80% delivery rate pales in comparison with a 0% rate if the vaccine is not selected for adoption. The debate on this issue has yet to be resolved. GAVI is working closely with countries to strengthen vaccine delivery and immunization services.

Information crucial for priority-setting is lacking. The final barrier to quickly changing the existing situation surrounding vaccines stems from a difficulty in identifying priorities. The underlying cause, however, of this difficulty is a lack of information which would help inform these prioritizations. Data is lacking in two key areas: on diseases themselves, and on the potential effectiveness of interventions (discussed below). It is extremely difficult to quantify the potential market for vaccines in terms of volume, and of who will be able to pay, and at what rate, without data. At the moment, the data on incidence of some diseases, on access to vaccines, and on workable delivery systems is not readily available. WHO has estimated that the incidence of yellow fever may be as much as 500 times greater than reported due to difficulty of diagnosis and lack of infrastructure. These considerations represent important variables which need to be understood in order to fully understand the potential market for a vaccine. Not having this information at hand makes it difficult to negotiate efficient and fair solutions for developing needed vaccines.

A lack of good understanding and information on the effectiveness of existing and potential interventions weakens the case for investment. Good data quantifying the effectiveness of existing interventions is similarly hard to come by. Were this data to exist, or be gathered and produced, it is possible that the case for increasing the investment in vaccine R&D would be significantly strengthened, at least from a public health standpoint.

Public-Private Partnerships Require Careful Management

The private sector may doubt follow-through The private sector's wariness in serving developing country markets comes from a combination of past experiences and current perceptions. The major historical factor playing into the private sector's decisions regarding working with the public sector to produce more vaccines, is the slow uptake of

[17] "Creating Global Markets for Neglected Drugs and Vaccines: A Challenge for Public Private Partnership." Global Health Forum I: Consensus Statement, February 2000.

certain current vaccines, like Hib, and Hep B, especially prior to the establishment of GAVI and the Vaccine Fund. Past and current uptake of current vaccines is the metric that industry uses as an indicator of the public value of vaccines, the state of distribution infrastructure, and of probable uptake. When a history of low uptake of current vaccines is compounded with specific instances in which the public sector asked the private sector to invest in a new (or different) vaccine, like heat-stable polio, and "changed" its mind after investments were made, the private sector's wariness in producing vaccines for promised future markets is understandable. Finally, the fact that the public sector is not one homogenous group, or does not represent one entity with which to negotiate, means that from the standpoint of the private sector, it can sometimes be difficult to reach agreement on issues and to initiate action.

The public sector may doubt motives. A number of important public sector groups have commented that the private sector is trying to take unfair advantage of the public sector through its negotiations. Certain public sector groups suspect the private sector is currently or will in the future use its oligopoly power to set prices, thus effectively denying access to developing countries. In numerous recent articles in the popular press, the private sector has been portrayed as charging exorbitant prices for drugs in the developing world. To date, the vaccine world has been less marred by these accusations and perceptions, but they remain important to note.

Public-private partnerships have their risks. Possible risks include perceptual issues, such as the concern that the private sector may try to "take advantage" of the public sector, or concern that the general public may question public funding of private sector activities, even if it is the best way to get results. For the public sector, it is difficult to achieve a balance between transparency and confidentiality in a competitive market. For the private sector, there are concerns that accepting public sector funds will entitle the public sector access to confidential information, may compromise intellectual property, or will slow the product development timeline. Perceptual risk aside, a major factor to be considered is that the public sector's funding of private activities necessarily changes the competitive landscape. By choosing one company to fund, the public sector runs the risk of discouraging other companies from continuing their investment in vaccine R&D, and thereby reducing the number of suppliers.

A number of steps may be taken in order to mitigate these risks. First, it should be noted that different types of interventions bring different risks, and different options for countering the risks. This topic will be further explored in the discussion on the range of possible interventions. Generally, however, there are a few steps that can be taken to mitigate risk. First, by pooling resources together (through alliances like GAVI and the Vaccine Fund) the public sector becomes much stronger, and therefore has an enhanced, and indeed legitimized position for negotiations with the private sector. In terms of concerns over transparency of use of funds, the burden lies with the public sector to clearly delineate systems for use, and to strive towards and enforce transparency wherever possible. Finally, the risk that the public sector intervention will alter the competitive landscape for the worse will be balanced by the current competitive system, which will make it difficult to subsidize one private firm at the expense of the others.

Part
2

Pushing and Pulling

R&D for "Near Term" Vaccines

Overview of "Push" and "Pull"

Two basic approaches to accelerate vaccine investment, development, and scale-up have been identified: "push" and "pull" mechanisms. Though different shades of definitions have been offered, the simplest define **"push" mechanisms, as those which reduce the risks and costs of investments**, and **"pull" options as those which assure a future return in the event that a product is produced**. Much work remains to translate the two concepts of financing and market creation into action. To date, a great deal of high level work has been done to outline possible approaches for public-private coordination, and creative financing mechanisms. However, very few of the strategies have actually been implemented on the scale necessary to assess their impact. Moving from rhetoric to action will require identifying and implementing a number of new mechanisms. Historically, the public sector has invested substantially in basic research "push" mechanisms, particularly basic research and some early product development. Less work has been done around pull mechanisms.

It has become increasingly clear that there is no "silver bullet." No one mechanism, either push or pull, will single-handedly solve the current vaccine problems. The basic issue is that while the end goals of the public and private sectors may be similar, the incentives or "ideal" situation of the two groups are diametrically opposed. For the public sector, the ideal scenario would be to avoid all risk, by only buying a product once it is developed, the demand is present, and the vaccine is available at a very reasonable price. For the private sector, however, the ideal situation would be one in which industry's risk is reduced through some agreement that "locks" the public sector into purchasing vaccine (probably at a specific price and quantity) before it is developed and produced.

In the following section, a menu of possible push and pull mechanism options is presented. Although each mechanism is described separately, it is likely that a combination of mechanisms will need to be used for each vaccine. The combination will need to be tailored for each specific vaccine, depending on the incremental costs and risks of that particular vaccine. While all of these mechanisms are focused on supply, all parties agree that creating demand – and the delivery systems to support that demand – is also a critical factor. The myriad considerations about demand and delivery systems are being considered by GAVI and elsewhere outside of this paper.

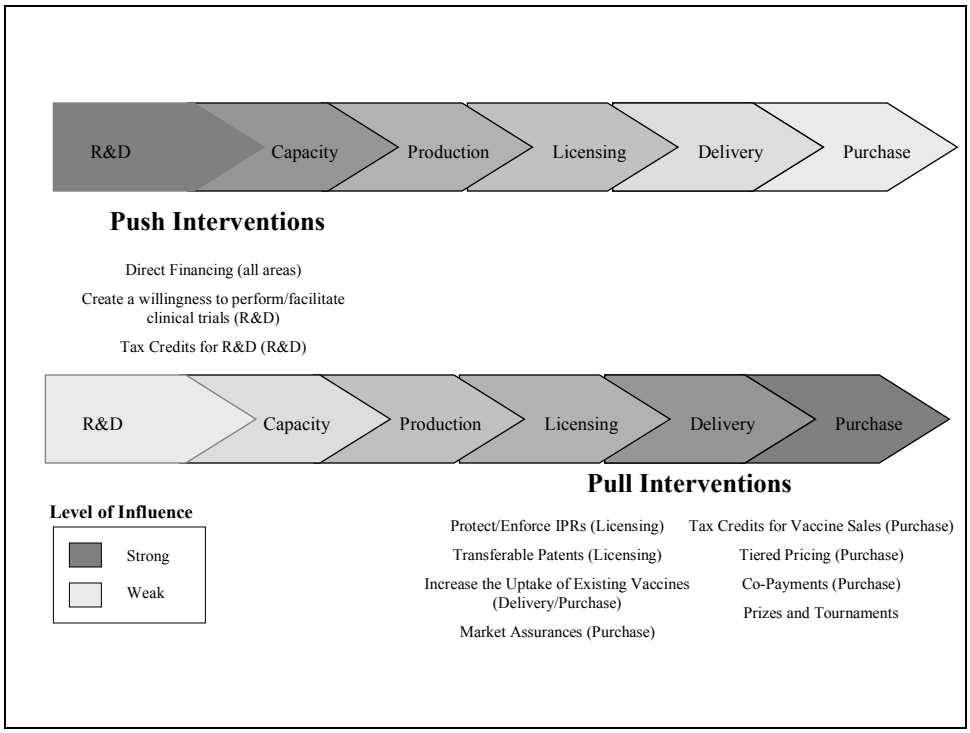


Figure 7: Push/Pull Mechanism: Push mechanisms exert greater influence early in the value chain, while pull mechanisms are stronger later.

"Pushing" the Product Through Development: Pluses, Minuses and Applications

Benefits Push options offer a number of benefits, the most important to which is that they reduce risk and thereby encourage investment where it might not otherwise occur. (e.g. by funding a clinical trial in a geography that a manufacturer has little incentive to choose). Another important benefit is the familiarity and proven track record of certain push interventions which have been successfully used in the past.

Drawbacks Certain types of push mechanisms (e.g. financing a clinical trial, or funding R&D on a specific strain of a vaccine) necessitate specifying or picking one candidate or project ("picking a horse"). It is possible that better options may emerge at a later date, or that manufacturers will drop promising candidates. A certain amount of loss must also be taken into account, as "picking a horse" early in the process means that some projects will fail. Other push options, however, like giving funding to help develop animal models, or to conduct field studies of natural exposure and resistance to disease, are basic and broad-based enough that they support all products being developed against a disease. Finally, push options do not promise an outcome, even though money is spent. Supported projects or products may fail, but the money will already have been spent, and in most cases will be irrecoverable.

Name	Description	Advantages	Risks
Direct Financing	Provide money to fund or directly implement activities necessary for vaccine development	Demonstrate public sector commitment Credible to industry because money is offered upfront Avoids need for specificity of desired product at early stage	Alters incentives ▪ Efficiency, cost ▪ May reduce number of candidate vaccines Hard for public sector to "pick a horse," and justify that choice Difficult to negotiate returns
Create a willingness to perform or facilitate clinical trials	Help facilitate trials Help inform on ethical considerations	Can help avoid costly delays	Sometimes viewed as "soft" intervention ▪ If used by itself, not viewed as a powerful tool Difficult to estimate its value, and therefore negotiate with manufacturers
Tax Credits for R&D	Governments (US and UK) offer tax credits (amount TBD) for research on vaccines	Credible to industry Familiar policy tool	Existence of a credit does not guarantee results May be difficult to implement and monitor

Figure 8: Summary of Push Options:

Direct Financing

Overview. Using direct financing as a push option entails providing money to fund or directly implement activities necessary to vaccine development. The main goal of this type of intervention is to increase the number of candidate vaccines, provide data required for wide-scale introduction, and accelerate the process towards the selection of the best, most efficacious vaccine. Public sector funds may go toward financing either non-product specific activities, or product specific activities. In the category of non-product specific activities, there are a number of areas in which the public sector has influence. The public sector can fund basic research on issues like the pathogenesis of a disease, disease burden analysis, diagnostics, potential vaccine presentation and, or correlates of immunity. The public sector can also help with information or funding on animal models and reagents. Finally, the public sector can play a role in helping the private sector to navigate regulatory requirements (see Box 4).

For specific products, the public sector has good leverage in product development and in licensing. There is a great potential for high value support in clinical trials, particularly the Phase III efficacy trials. This phase of trials is typically the most expensive. The private sector has been willing to fund trials relevant for licensing the vaccine in industrialized countries, but not necessarily in developing countries. Not only are developing country trials costly, but on occasion they can generate data or negative PR that can threaten licensing. Looking forward, there is a good opportunity for the public sector to fund, or partially fund trials in these areas, as well as to help manage problems (PR and otherwise) that may arise. The other area that the public sector could help finance is scale-up. Depending on the vaccine, the costs of scaling up production to meet developing country demand may be disproportionately high. Without public sector help, the private sector may be unwilling to incur these costs.

Box 4. Understanding Regulation

Regulatory requirements are becoming increasingly stringent, and preparation of applications of for marketing authorization is hampered by the differing requirements across countries. With the exception of some countries served by UN agency procurement, manufacturers must obtain separate authorizations for each market in which they propose to sell vaccines, a long and costly process. This barrier could be addressed, at least partially, by harmonization of requirements of regulatory agencies, exemplified by common formats for data submission, common requirements for data, and mutual recognition agreements among countries with similar epidemiological characteristics. The public sector can (and does) help by actively encouraging harmonization, and by promoting simplified licensing arrangements for products prequalified by WHO.

A second issues is the increasing difficulty of finding appropriate regulatory pathways for developing market vaccines produced in the United States and Europe. Both the FDA and the EMEA[18] have a responsibility to their home markets, and their ability to evaluate the suitability of a product for these markets is based on use of experts familiar with the characteristics of these markets. In cases where a product is specifically tailored to developing country needs, it is understandable that evaluation of clinical data might require additional expertise. Nevertheless, these agencies have important regulatory expertise on production, consistency, adventitious agents, testing, to name a few areas, which could be extremely useful in an evaluation of these products, and, some would say, a responsibility to apply this knowledge even for products that would not be marketed within their borders. The public sector is currently actively working on defining appropriate regulatory pathways for these products, in consultation with the FDA and the EMEA, and with other strong regulatory authorities around the world. The success of these efforts will be critical to the future development, production, and regulation of critical products such as vaccines against malaria and AIDS.

Advantages and risks. Direct financing is a powerful mechanism because it is an immediate demonstrated public sector commitment that goes beyond spoken promises. It also has the advantage of avoiding the need to commit to a specific price or quantity of vaccine.

On the other hand, direct financing runs the risk of changing incentives in a way that works against the objectives of timeliness and efficiency. If manufacturers know that all the costs associated with a clinical trial will be funded, for example, the incentive to work quickly and

[18] European Agency for the Evaluation of Medicinal Products

in the most cost-efficient manner is somewhat diminished. Furthermore given the difficulty of "picking a horse," the public sector runs the very real risk of choosing the wrong one, and having dispensed money with nothing to show for it down the line. Negotiating the appropriate level of return once the product is fully commercialized can be difficult. There is also the risk, that the public sector, by selecting one specific company to fund, changes the competitive landscape in a way that does not encourage competition, therefore reducing the number of candidate vaccines. Finally, as discussed above it is often difficult for the public sector to justify paying the private sector.

Facilitating Research

Overview Aside from providing money, there is an important role for the public sector to play in two other areas of clinical trial work: facilitation of the trials and adherence to ethics. Potential roles for the public sector include: working with local officials to inform and educate country participants of the need for and importance of clinical trials, and assisting in handling any problems that arise during the trial. The first role, education, is extremely important, particularly for diseases like HIV/AIDS and malaria. Enrollees need to understand that participating in the trial will not necessarily protect them against the disease, and equally importantly, that if they do contract the disease, their participation in the trial is not necessarily the cause. The public sector could help manufacturers to ensure clarity around issues of follow-on access. It is not uncommon for clinical trial participants to assume that their community will have guaranteed and timely access to a vaccine. However, as the time between a clinical trial and licensure of a vaccine is often lengthy, and the introduction of a vaccine into developing countries even longer, this expectation needs to be addressed.

Advantages and risks Although fewer "real" dollars are tied to educating community and trial participants when compared with other push mechanisms, its importance cannot be underestimated. Indeed, clinical trials are most successful when time has been taken to build political and community support. Despite its importance, this type of community intervention is sometimes viewed as "soft" and therefore less important. It is unlikely that this mechanism, by itself, would be viewed as sufficiently valuable to alter investment behavior. A final drawback is that the difficulty of estimating the value of this intervention makes it very hard to negotiate with manufacturers

Tax Credits for Vaccine Research

Overview. Structuring tax credits to encourage vaccine R&D is another push intervention under consideration. The U.S. and the U.K. are both in the process of preparing legislation for introduction. In the United States, a bill proposing a 30% tax credit on R&D for vaccines against malaria, TB, HIV/AIDS and any other disease of a single etiology that kills more than one million people a year, is being prepared. The bill allows large companies to take a 100% credit on R&D work that they contract out to smaller companies. Additionally, the bill includes a provision for companies (like small biotech startups) that have no tax liability (because they are not yet making a profit) to receive a refundable tax credit (provided they might certain specifications like less than $500MM in revenue, and no tax liability for the past three years). The current bill amends a provision of an existing bill which allows for a tax credit of 20% against income tax for R&D expenditures (not specific to vaccines). The current vaccine-specific provisions were introduced originally during the 106th Congress in 2000, but failed to pass either the House or the Senate. However, observers believe that the current bill has a strong chance of passing in the 107th Congress, although the Bush Administration has not yet taken a policy

stance on this issue. In the U.K., Chancellor Gordon Brown announced plans for a similar tax credit. Under the U.K. proposal, the government will offer new tax breaks to drug companies to encourage research on "cures for the most lethal diseases afflicting the Third World." [19] Chancellor Brown is also proposing changing the tax system to encourage donations of drugs and vaccines for these diseases.

Advantages and risks. Like direct financing, tax credits have the benefit of being a familiar policy tool with a proven track record. The tax code of the United States currently contains an allowance for a 20% credit on R&D expenditures and though it must be renewed on an annual basis, it is non-controversial and nearly unanimously supported by members of Congress and industry.. Proponents of expanding the credit for vaccines believe that chances of passage are great if the legislation takes the form of an amendment to this existing and well-understood credit. Credible or not, however, there remain two issues with using tax credits for vaccine R&D as a push mechanism. First, like other push mechanisms, the existence of the credit does not guarantee results. The second consideration is the question of how the bill will be monitored and implemented. The authors of the bill are currently looking at ways to ensure that the Treasury and the IRS will be able to enforce the provisions of the bill and avoid inadvertent or deliberate non-compliance, such as erroneous bookkeeping or claiming the credit for basic research which could be applied to pharmaceutical or vaccine products, other than vaccines against the three target diseases.

Creating Markets to "Pull" Products: Pluses, Minuses and Applications

Benefits. For the public sector, pull mechanisms seem to be a safer form of intervention, if structured so that money is only given in the event that a desirable, affordable or specified product becomes available.

Drawbacks. If structured so that commitments to specific products must be made early, the major problem of pull mechanisms is the difficulty of being specific about desired outcomes and returns far in advance of having an actual product. It is very hard for the public sector to choose one "winner" and justify that choice to the public (and also members of the private sector) before an actual product exists. Similarly, it is difficult to agree to a price before a product is licensed. If a "winner" is chosen, and a price is agreed to, the public sector runs the risk of being "locked-in" to an outcome that may or may not be best. From the standpoint of the private sector, pull mechanisms place them at the mercy of political "changes of heart." For manufacturers who must invest early and heavily, political "changes of heart" have serious financial implications. Finally, the fact that these mechanisms have not been tested increases their risk factor. Without a historical record to consult, it is unclear how results will be measured and monitored.

[19] *The Daily Telegraph*. February 27, 2001.

Name	Description	Advantages	Risks
Increase the Uptake of Existing Vaccines	Use public sector funds to buy existing vaccines which have not had high adoption rates	Sends a clear signal to industry about public sector seriousness	Does not deal with specific product, so may not be enough to correct problems
Prizes and Tournaments	Offer cash or other prizes to whoever achieves a certain pre-specified goal (prizes), or progresses farthest in research by a given date (tournaments)	Encourage competition, and therefore may increase potential number of candidates Easy to implement May result in good public relations	Industry may not be enthusiastic about competing for prizes/tournaments Do not guarantee a result, but prize/award must be made nonetheless
Transferable Patents	Give a manufacturer the right to extend the patent on any product in an industrial market, or Allow a manufacturer to extend the customary time period that a patent is protected	Captures attention/interest of big pharma May trigger a "trickle-down" effect in smaller companies	Tends to favor big companies despite "trickle-down" effect Users of other drugs may not want to "subsidize" vaccines Political/legal difficulties of transferring patents
Co-Payments	An amount of money (probably not equal to the full price of the vaccine) is offered to manufacturers for every dose of vaccine sold	Credible to industry (on existing vaccines only) because payment is made today rather than in the future Public sector avoids having to negotiate the full price of the vaccine	Difficult to determine appropriate amount of co-pay May not be enough of an incentive to industry May create expectation that the co-pay is equal to the price

Figure 9: Summary of Pull Options: Continued on next page

Name	Description	Advantages	Disadvantages
Market Assurances	Public sector promises to buy vaccines if produced (conditions may vary)	Reduces risk to manufacturers, therefore creating incentives	Industry may not view promises as credible Industry may view commercial return as too distant or discounted to be worthwhile For public sector, big opportunity cost of putting money up upfront
Intellectual Property Right (IPR) Enforcement/Protection	Public sector makes commitment to enforce protection and enforcement of IPRs	Provides continuing incentives for industry to invest	Difficult to implement Difficult to enforce May be politically unpopular with those who say cheap drugs are a right
Tax Credits for Vaccine Sales	Government offers a 100% tax credit on vaccine sales to manufacturers; bill has a $1 billion cap	Familiar and credible policy tool Money only spent when product is produced	May be inflationary Industry may deem returns too far in the future to offer incentives May be difficult to determine level of credit Unclear how prioritization will be made if $1 billion cap is reached

Figure 9: Summary of Pull Options

Accelerating the Uptake

Overview. Increasing the uptake of existing vaccines sends a clear signal to industry that the public sector is committed to introducing new vaccines, and therefore credible in calling for increased investment from industry. As previously discussed, the uptake of current vaccines is a major factor from which the future potential of vaccines is extrapolated.

Advantages and risks. The strongest advantage of increasing the uptake of existing vaccines is the clear credible signal sent to industry about the seriousness of the public sector's intentions. The presence and immediate allocation of real money is the best way to prove credibility. This mechanism, however does not address the specific concerns of the vaccine needing attention, and so it may not by itself be enough to correct the problems.

Prizes and Tournaments

Overview. While structured slightly differently, prizes and tournaments have similar advantages and risks. Prizes are generally offered to whoever achieves a certain pre-specified goal or product, while tournaments generally offer a reward to whoever has progressed farthest towards the target by a given date. The size of the prize should generally correspond to the size of the investment required to win.

Advantages and risks. Both mechanisms have the value of encouraging competition, and therefore increasing the number of potential vaccine candidates. They are also relatively easy for the public sector to implement. For the private sector, valuable positive public relations may be a side-effect of winning a prize or a tournament. Problems, however, include the fact that industry may not be enthusiastic about the idea of competing for prizes or in tournaments. Industry representatives have commented that they are "in the business of making vaccines, not winning prizes." Another serious drawback to prizes and tournaments is that holding them does not guarantee that a viable, affordable vaccine will result, however, the prize, or tournament prize must be given to the winner, no matter what is developed.

Extending and Transferring Patents

Overview. Transferable patents would give a manufacturer the right to extend the patent of any product (not necessarily on a vaccine) in the firm's portfolio in several large industrial markets. Extending patents would allow vaccine manufacturers an extension on the customary time period that the patent is protected.

Advantages and risks. Transferable patents are a powerful mechanism because they extend the revenue stream of blockbuster products. They capture the attention and interest of large pharmaceutical players, and may also trigger a "trickle-down" effect as pharmaceutical and venture capital companies may increase investment flows to smaller firms in hopes of capturing a share of the potential revenue. This "trickle-down" effect in some ways mitigates a disadvantage of transferable patents, which is that they tend to favor large pharmaceutical companies which are more likely to have "blockbuster" drugs. It is likely that smaller start-ups would not have a product that would benefit from a patent extension. One option that has been proposed is to offer the vaccine manufacturer an extension on the patent of the vaccine in question. Making the patent extension of the vaccine of equal value to a transferable patent on a blockbuster may require different time

tables (e.g. 1 year for patent transfer for highly profitable drugs, and 3-5 years for patent extensions on priority vaccines). Beyond ironing out the specific details of how patent transfers or extensions might be implemented there remain two significant issues. First, the willingness of consumers to essentially subsidize vaccines by accepting higher prices on their patented drugs is unknown. Second, the difficult political and legal implications of implementing this mechanism present a serious roadblock. In order for a patent to be transferred or extended, major exceptions to patent laws must be taken in each country in which the patent would be affected. These exceptions are not likely to be politically popular.

Co-Payments

Overview. A co-payment – probably some amount not equal to the full price of the vaccine – is offered to manufacturers. The public sector could guarantee some fixed amount to pay, but not necessarily lock-in to a particular price for vaccine.

Advantages and risks. Co-payments are attractive to industry because they are viewed as a commitment today, which is more credible than a promise for future payment. They are attractive to the public sector because the public sector avoids having to agree to or negotiate the full price for a vaccine. However, it is unclear how the "correct" co-pay amount is to be derived, and if the co-payment amount, which could end up being a fraction of the vaccine price, would offer enough of an incentive to industry. There is the danger that the co-pay may create an expectation that it is equal to the price. Finally, it is not clear that offering co-pays is viewed as a credible mechanism by industry when the co-pay is proposed for a vaccine not yet produced.

Differential [Tiered] Pricing

Overview. Differential pricing refers to the practice of selling vaccines at different prices in different markets. In order for differential pricing to work, the vaccine market must be high volume, and segmented by purchasing power. There must be minimal risk of parallel imports, and a willingness to accept and enforce differential prices, particularly in the markets with the higher prices.

Advantages and risks. Differential pricing is currently the only mechanism that allows affordable access to a vaccine in developing and industrialized countries. In many cases the time delay before the product is fully "mature," and enters developing countries is twenty years. It allows industry to recoup its investments on a vaccine, while still offering the product in developing countries. By allowing industry to make a profit, tiered pricing provides incentives for industry to invest. Finally, differential pricing is a familiar mechanism, as it has been used in nearly ever other sector from toothpaste to batteries. It has a history of being not only accepted, but also viewed as essential for growth. Differential pricing, however, is difficult to implement. Safeguards must be instituted to prevent lower developing country prices from flowing back into wealthy markets. In developing countries safeguards must be put in place to prevent the elite from benefiting from the lower public sector prices. Once the lower price is established, industry runs the risk that the lowest price becomes the index, towards which industrialized countries negotiate. Finally, political agendas can be very damaging to attempts to institute differential pricing. In order for tiered pricing to succeed, governments, the public, and politicians in industrialized nations must be willing to pay more for vaccines than developing countries. In the US, this has not always been the case. Since 1982, when Congresswoman Nancy Hawkins called Merck before Congress and questioned them as

to how they could justify charging the U.S. government nearly three times as much as PAHO for vaccines, U.S. manufacturers have not been very interested in submitting bids to Unicef to supply vaccine to developing countries.

Market Assurances

Overview. Market assurances are a type of "guaranteed" off take. The assurance may be structured in a number of different ways, depending on certain conditions: promises to a specific manufacturer based on pre-agreed terms, or to the first firm able to develop or manufacture a product with specific characteristics. Three variables that may be part of a manufacturer guarantee are (1) production of a specific product, (2) production of a specific number of doses, or (3) agreement to purchase over a specific timeframe. Each of these variables may be a part of a market assurance contract/agreement. The promises made may be backed by either "soft" or "hard" money guarantees. The overriding issue is the trade-off between opportunity cost and credibility: money put aside now is the most credible to industry, but it obviously carries with it the highest opportunity cost.

Advantages and risks. The major advantage of market assurances is that they reduce risk, and therefore create incentives to investment in vaccine R&D. Major issues include, however, the question of whether or not industry will consider a promise made by the public sector to be credible. Although market assurances can be structured so that they are technically legally binding, in reality it is hard to imagine how they would be enforced in the event that the public sector reneged on its promise. Issues of credibility aside, industry may deem the commercial return to be too distant and discounted to be worthwhile. Perceptions vary by product, (e.g. for HIV/AIDS returns are thought to be very far in the future, while for other diseases they may be nearer) but the issue remains. In order to establish credibility, the public sector may need to put up money upfront.

Intellectual Property Right (IPR) Enforcement/Protection

Overview. The public sector could potentially make a concerted commitment to enforce IPRs. IPRs are the foundation upon which the profit of pharmaceutical companies is based. When IPRs are violated, the incentives for industry to invest in vaccine R&D are greatly diminished. The public sector has already taken steps in this direction (e.g. setting up the WTO to enforce the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) but improvements remain to be made. Another option proposed by Harvard professor Jeffrey Sachs in April of 2001 concerns using development aid to help developing countries set up systems to protect and enforce IPRs.

Advantages and risks. Simply put, ensuring the enforcement of IPRs provides continuing incentives for industry to invest in vaccine R&D, development, and distribution. IPRs, however, are difficult to implement, difficult to enforce, and politically very unpopular with those who contend that cheap drugs need to be made available to bridge the gap between the "haves" and the "have-nots." Questions remain about whether or not it will be possible to enforce TRIPs, and whether by itself this mechanism provides enough of an incentive.

Tax Credits for Vaccine Sales

Overview. In the U.S., a bill on tax credits for vaccine sales is being prepared for introduction. In the draft, international manufacturers would be given a tax credit equal to 100% of the price of the vaccine, if and when vaccines against malaria, TB, and HIV/AIDS were produced. The proposal includes a $1 billion dollar cap. In current drafts, this pull mechanism is being included with the legislation being prepared on tax credits for R&D discussed above (push mechanism).

Advantages and risks. Like tax credits for vaccine R&D, tax credits for vaccine sales have the advantage of being perceived as a credible and familiar policy tool. In contrast to tax credits for R&D, however, tax credits for vaccine sales do not create tax revenue losses in the current year, which is attractive to the government, though not necessarily to industry. From the standpoint of the public sector, tax credits are attractive because money is only spent once a product has been developed and sold. The downsides, however, are many. First, industry has not expressed much interest in discussions on the topic. From industry's perspective, tax credits on vaccine sales are an incentive offered too far in the future to merit investing hundreds of millions of dollars in research that may not even lead to a vaccine. In the event that a tax credit is enacted, it may be difficult to determine the appropriate level of credit. In the case of the U.S. proposal (100% credit) in particular, but also probably applicable to other levels of credit, the credit would likely prove inflationary, as industry would have no incentive to keep the price of the vaccine low. Finally, it is unclear how priorities will be set in the event that a number of these vaccines become available simultaneously, all competing within the same billion dollar cap.

Part

3

The Project

R&D for "Near Term" Vaccines

Project Goals and Objectives

An essential goal of GAVI is to accelerate the development, production scale-up, and distribution of three near-term vaccines. Over the next two to three years, we intend to identify the financing mechanism, or combination of mechanisms, which will best address the current "market failures" as outlined above, and then to implement these mechanisms. GAVI partners believe that they can best achieve their objectives by not only strengthening and expanding the delivery of existing vaccines, but also by harnessing the complementary product expertise of both public organizations and private firms. The GAVI Board has mandated that partners move the public-private sector discussion from rhetoric to action, identifying and addressing the scientific, financial, logistical, and policy hurdles currently blocking the rapid development and use of new vaccines in the developing world.

GAVI seeks to focus on near term vaccines in order to maximize impact and to learn from the implementation. This work will develop a "track record" and a level of trust between the public and the private sector. The lessons learned from these vaccines will pave the way for the high risk but high priority vaccines of the future --- vaccines which will prevent AIDS, malaria and tuberculosis.

Project Action Steps

Selecting Diseases

To select vaccines for this project, the GAVI R&D Task Force used a number of criteria, all taking into account the desire to focus on near-term vaccines. In no particular order, the following criteria were/are all taken into account in selecting diseases:

- disease burden in the developing world
- scientific feasibility of developing vaccine
- projected time needed to have a vaccine available for use in developing countries
- whether alternative public health measures are available to prevent infection
- whether an effective treatment exists

- public perception of the disease and of the need for its control[20]

An additional criterion was that the disease be one which plagues primarily the developing world, and is therefore not given the attention or resources of those that occur commonly in the developed world. The three vaccines chosen were/are meningococcal A conjugate, pneumococcal conjugate, and rotavirus.

Current and Proposed Implementation

GAVI partners though each of the Task Forces will address the barriers to rapid development, scale-up, and affordable prices with the involvement of public and private manufacturers and technical experts. As part of a larger overall work plan, public and private manufacturers, technical experts, and previously-identified "vaccine teams" will together identify push and pull strategies which will overcome the identified gaps, recognizing that a combinations of push and pull mechanisms will probably be necessary. The next step is to work with individual manufacturers to identify specific barriers limiting the rapid development of their vaccine. Cross-cutting ideas will be discussed with a number of potential funding bodies including key bilaterals such as the Netherlands, Norway, Canada and the US, World Bank IDA, the Gates Foundation, GAVI, Vaccine Fund staff, and others.

The "Out of the Box" group, a strategic and high-level working group of 10-12 individuals from the worlds of finance (in the public and private sectors), development agencies, the pharmaceutical industry and philanthropic foundations is being convened. The group members, brought together in their individual capacities under the auspices of GAVI, will bring a unique set of skills to the public health community, including a better understanding of the economic and financial motivations and markets, the creative power to break out of old molds, and the personal and institutional credibility to lead others to adopt new strategies. [On behalf of GAVI, World Bank President James D. Wolfensohn has invited select individuals to participate in the first "Out of the Box" meeting in the second semester of 2001. See Annex 2 for a list of members.]

Work is already underway. The World Bank is working with McKinsey and Company to perform a study on quantifying the benefits of alternative finance mechanisms. The study, which is divided into two steps, is designed to analyze the incremental costs and risks of supplying vaccines to developing country markets. This basic understanding will then be used to help both the private and the public sectors to prioritize and tailor interventions, so that public sector funds are best leveraged. Step I, an interim high-level analysis of incremental costs has been completed. Step II in which specific interventions will be quantified, is scheduled to take place in the fall.

Demonstrating the Effectiveness of Financial and Market-Based Solutions

A critical part of the work is to monitor, in as quantifiable a fashion as possible, the effectiveness of the financial and market-based solutions that are selected. Possible indicators could include, for instance, the number of years before a certain percentage of coverage is achieved in developing countries. It will be quite difficult to measure impact because that which it is being measure against is hypothetical (i.e. it is not clear that in the absence of creative interventions anything will be done, so it is difficult to establish a benchmark or case to compare to). Nonetheless we intend to be as rigorous and quantitative as possible in assessing the value-added of the techniques

[20] Levine, Myron M., M.D. D.T.P.H, "Issues and Opportunities for Consideration by the Global Alliance for Vaccines and Immunization (GAVI) in Addressing its Research and Development Objectives."

which we choose to implement against more traditional techniques. Finally we hope also to explore generic issues associated with the effective use of these techniques. Our goal is to be able to extrapolate lessons from these near –term vaccines that can be applied to malaria, TB, HIV/AIDS, and vaccine development in general.

Process and Implementation Issues

A project team is currently being assembled. The proposed structure is designed to bring new financial expertise to the broad scientific, technical, and policy skill base represented in the immunization community. The project team will include two project co-leaders, one part-time and one full-time, and a project coordinator to manage the vaccine teams, problem-solve issues associated with the implementation of the work plans, work with the Core Group on specific issues, and coordinate the communication and interaction with the Financing Task Force. Vaccine Implementation teams will be composed of the partners (manufacturers and technical and country experts) who have taken a lead on these products. (For example, a meningococcal team, supported by WHO and Gates CVP is already in existence).

The "Out of the Box" Group will be convened twice yearly to offer their insight into the project.

Mobilizing its unique combination of expertise, the "Out of the Box" group could be effectively used to review the proposals, and to choose among one of four recommendations to GAVI partners: strong endorsement for the GAVI partners to identify funding; provisional endorsement, conditional on certain clarifications or modifications; re-review after additional analytic work; or strong reservations. In evaluating the proposals, the "Out of the Box" group would be asked to think broadly about the longer-term and non-financial impact of different finance arrangements, as well as the "fit" of the proposals with the overall goals of GAVI partners.

The existence of this core group of experts will bring new and creative ideas to our thinking, add rigor to our process, and provide the high level validation which will be useful in gaining the buy-in of the immunization community.

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