Assembling a Global Vaccine Development Pipeline for Infectious Diseases of the Developing World

Abstract: 120 words
Text: 3316 words
References: 11
Figures: 3

Abstract

Commercial realities drastically reduce private investment into the development of new public health tools, but increased awareness of this has resulted in the emergence of a variety of research-based, not-for-profit organizations. This article reviews current vaccine developments and sets a framework for efficient R&D investments in this area. Several key “Push” and ”Pull” factors within the vaccine Research and Product Development (R&PD) landscape are identified and their impact discussed. The concept emerges of a Global vaccine pipeline affected by these driving forces and composed of all the individual vaccine initiatives and global partnerships. All partners should work together to establish and promote a global, sustainable research and development pipeline delivering optimal vaccines and immunization technologies for public health priority diseases.

Need for Vaccine Research

Vaccines are the cornerstone of the fight against communicable diseases, as demonstrated by, among others, the success of smallpox eradication, the drastic reduction in polio cases over the last twenty years, the progress towards tetanus elimination and reduction of measles mortality. In spite of these achievements, infectious diseases are still responsible for close to 30% of all deaths worldwide, with more than 15 million people dying every year, mostly in low- and middle- income countries[1]. Around 1.5 million of these deaths could be averted if currently available vaccines were universally applied. In addition, many childhood killer diseases do not yet have licensed vaccines (Figure 1[2]).

Achievement of the United Nations (UN) Millennium Development Goals (MDGs) requires research and product development (R&PD), innovation and breakthroughs to rise to the challenges set. Goals, such as halving current child mortality figures by 2015 (Goal 4), combating HIV/AIDS, malaria and other diseases (Goal 6), forging a global partnership for development and partnerships ensuring access to medicines (Goal 8) are highly pertinent to the vaccine community. In 2005 the World Health Assembly adopted an ambitious and comprehensive Global Immunization Vision and Strategy 2006-2015 (GIVS) to fight vaccine-preventable diseases[3]. GIVS has three main aims: to immunize more people against more diseases; to introduce a range of newly available vaccines and technologies; and to provide a number of critical health interventions with immunization. By contributing to a reduction in the burden of disease, new and improved vaccines and improved accessibility to old and new vaccines alike will contribute substantially to the global efforts to achieve these objectives and in so doing reducing global poverty (see Figure 1).

Driving forces for Research and Development

The R&PD process bridges the gap between scientific discovery and the delivery of tools for health intervention. Vaccines used today are the product of discovery and development of past decades. The aim of the R&PD processes is to design effective and robust methods for the identification and production of potential vaccine candidates, to test them for safety and efficacy in preclinical models, and finally to establish their efficacy in humans. There is a clear responsibility throughout vaccine development both to adhere to and be guided by a structured framework embodying registration

requirements and normative guidelines that collectively assure the ethics, safety, and quality of the research, manufacturing, and clinical development steps in the R&PD process. It often takes more than 10 years to arrive at a final licensed vaccine,[5] requiring not only excellence in R&PD but also managerial and funding commitment throughout the endeavour. The cost of developing a vaccine from research and discovery to product registration is estimated at between $200 million to $500 million US dollars per candidate.[6] This figure accounts for the failed candidates which had to be abandoned during the development process. In short, vaccine R&PD is lengthy, complex and loaded with binary outcome risks.

Several driving forces impact upon the R&PD process targeting vaccines intended for essentially no- or low-profit markets. They can broadly be grouped into two categories referred to below as “Push” and “Pull” forces or drivers, terms commonly used for developing business strategies (Fig. 2). Thus, in abstract terms, a product is developed either due to a clear demand, i.e. a “pull”, for the vaccine in the marketplace or because it becomes technically and operationally feasible, i.e. a “push”. In practice, the actual delivery of the product to the population in need is dependent upon the concerted action of both "push" and "pull" forces (see Figure 2).

Within the context of vaccine development, push forces are principally composed of scientific and technological advances, management and coordination support structures and availability of R&PD funding. Pull drivers reflect the forces resulting from governmental and public recognition and commitment to fulfilment of health needs, as well as from the potential profitability of a future product within a specific, free-market segment.

To establish a sustainable product pipeline consistently yielding new vaccines and contributing new tools to improve public health, a balance of both push and pull forces is needed. In addition, the reality of these forces needs to be credibly articulated in language that resonates with all stakeholders involved. Investment of resources and efforts in strengthening any of the push and pull forces can affect the product-oriented pipeline and the impact of unilateral, or asymmetric, disturbances, to any particular point of the process should be viewed holistically within the context of the entire development environment. In a commercial world all the push forces are united by company operations targeting either existing or emerging markets. In public funded research additional complexity arises from the existence of numerous, independent entities each

with their own discrete mandates. Below, we overview the current status of the R&PD driving forces associated with the global vaccine pipeline.

Technology Push

In the past few decades, scientific advances in fields such as biotechnology, immunology, bioinformatics, genomics or proteomics, as well as the development of DNA and peptide-based vaccine technologies have provided huge numbers of potential new products at the entry point for vaccine target selection and development. Preclinical vaccine candidate testing platforms as well as new approaches to the development of disease animal models (such as transgenic animals) have moreover broadened the range of potential approaches to vaccine target validation. Finally, innovative drug delivery methods and improved understanding of pharmaceutical formulation and clinical testing allow the potential enhancement of both existing and candidate vaccines. Several publicly funded, broad-mandate research funding entities, such as the USA-NIH, UK-MRC, USAID, IVR, TDR, PATH, IVI (for abbreviations see legend to Figure 3) and others, are currently active in this arena.

Using technology as the departure point for promoting collaborative initiatives is very appropriate. With the technology acting as a common language, exchanges between developing and established health promoting initiatives (both North-South and South-South) can be readily established. The ultimate goal of these networks is to bring to focus collective research efforts upon the challenges present within disease endemic countries. In this manner, by aligning the levels of awareness of all stakeholders, the effective engagement of all research communities can ensure that the most health-relevant issues are addressed using the most effective technological approaches available.

R&PD Funds Push

Developing countries' public spending on R&PD is insufficient to support effective internal development for new or improved tools to combat the wide spectrum of infectious diseases prevalent in these countries. The low capacity resulting from internally-derived funds has recently been bolstered by a positive trend in contributions from industrialized countries to the developing world. Examples of this type of funding are seen from bilateral development agencies such as USAID, CIDA-Canada, DFID-UK, SIDA-Sweden (for abbreviations see legend to Figure 3) and others, from multilateral

organizations such as WHO, UNDP, the World Bank, the European Commission, and from public and private foundations and grant support programs such as those of the USA-NIH, the Rockefeller Foundation, the Wellcome Trust or the Bill and Melinda Gates Foundation, among others. Despite this increase, R&PD funds directed to vaccine research are still perceived as being insufficient.

Management Push

Effective vaccine R&PD relies on efficient management structures with access to long-term committed resources. In the absence of effective and experienced management, successfully guiding a product through the complex and lengthy process required, vaccine development is virtually impossible. Several international initiatives, public-private partnerships and alliances active in vaccine R&PD, such as TDR, PATH, IVI (for abbreviations see legend to Figure 3), have been created in the past two decades. Several single-disease focussed entities, such as Aeras, IAVI, MVI (for abbreviations see legend to Figure 3) have been established with a goal to manage the product development processes. In addition to these targeted initiatives, many established programmes and dedicated international and national institutions provide *ad hoc* support, advocacy and funds for managing vaccine R&PD projects.[7] Often, these new R&PD initiatives (IAVI as an example) take charge of all product-related push forces (technology, funds and management) supported by fundraising and advocacy, although for the most part the link to control programs and procurement realities needs still to be effectively integrated.

Market and procurement funds availability Pull

At present all publicly funded vaccine R&PD require the involvement of at least one industrial partner or at a minimum of one established manufacturing entity, as a result of the capital expenditure barriers resulting from the need to produce vaccine candidates according to Good Manufacturing Practices (GMP). Within the operations of the industrial partner, factors impacting upon the minimum level of pull drivers required to attract significant investment are similar for products intended for the developing world or for an established market economy. These factors include developmental and commercialization costs and risks, culminating in the risk-adjusted chance of generating acceptable stakeholder return from a finite budget. Throughout the decision making process directing the choice to favour one development program over another the

concept of "opportunity cost" prevails i.e. the value of using resources in one way versus the value of pursuing other available alternatives. The minimum acceptable market pull forces in a public-private partnership are perceived by the commercial third party as being at the very least where the opportunity-cost is neutral. The public sector realizes a need to take into consideration the expected return of a specific investment in terms of public health gain, as compared with investing always limited resources into competing priorities. For example, GAVI is currently developing and testing framework-based, investment cases for future fund allocation. The combination of the developmental and manufacturing risks compounded by the political and economically-driven structural uncertainties in the end-consumer marketplaces collectively often result in unattractive investment propositions for commercial vaccine development organizations (for a review on vaccine supply analyzes see ref. 8).

To overcome the vacuum left by the lack of an innate market pull, public funds have been proposed to be set aside to guarantee procurement of new vaccines at a fixed-price and during a pre-determined time period. By reducing uncertainty in the commercialisation risk well in advance, developmental risk becomes the main variable to consider in the managerial decision making process. As a result of the de-risking effect of this policy the inclusion of public-good vaccines within a commercial product portfolio should be facilitated. As an example of the effectiveness of this approach, public sector increase in procurement commitments and funding has been successful in attracting commercial entities to invest in the development and production of relatively low-cost HepB and combination vaccines for developing markets. This may be followed in the coming years by investment into rotavirus and pneumococcal vaccines upon their introduction.

Control Priorities and Health Systems Capacity Pull

National governments are the key players in the formulation and implementation of national immunization policies. Public sector entities such as international organizations and disease control programs should therefore provide countries with sufficient information about disease burden and cost-effectiveness or cost-utility of new vaccines to enable governments to take evidence-based decisions about the introduction of new vaccines into their immunization programmes. As a result of clearly articulated and consistent national program policy statements on new vaccine introduction, backed up

by recommendations from international partners, global demand for new products can be better ascertained and used as a pull factor to stimulate vaccine R&PD.

In addition, major investment is required for the strengthening of health systems prior to the introduction of new products. Indeed, many developing countries health systems are struggling to even sustain their existing vaccine programs. Currently, many international agencies, alliances, NGOs and bilateral initiatives focus on helping national governments to strengthen their immunization and health systems. The main international players in this arena are WHO, UNICEF, The World Bank, GAVI and VF (for abbreviations see legend to Figure 3). It is hoped that future strengthening of health systems will overcome this capacity barrier and lead to the development of a more dependable pull force for vaccines R&PD efforts.

Advocacy Pull

If effectively elaborated, evidence-based advocacy can have a great impact in attracting the attention of researchers and funding bodies to public-good vaccine development projects. Surveillance data, global and national burden of disease estimates and demand projections can emphasize the true health value and depth of particular markets attracting R&PD investments. Through this process, under-served diseases may potentially be rendered more attractive markets for commercial development and have an increased likelihood of attracting public funds and management efforts. Advocacy support is therefore important for the sustainability of R&PD programs as well as for the delivery of non-monetary credits for all partners contributing to the enterprise.

The existence of all the push and the pull forces as well as an appropriate balance between them also is required for establishing a sustainable product pipeline. Several independent product candidates should be “pulled and pushed” into the pipeline to beat the odds of research product attrition rate dictated by probabilities of success, resulting eventually in at least one licensed product being launched. The driving forces should not favour one vaccine candidate or one clinical trial project but the whole product pipeline of numerous projects, promoting fair competition and diversification of research approaches. This will result in the establishment of successful sustainable pipelines (see Figure 2) of research projects to deliver tools and research support projects for future efficient global immunization efforts.

The imbalance of forces, or lack of one or some of them, impairs the formation of an efficient R&D pipeline. As in the case of malaria vaccine R&PD, the existence over the past decades of effective push forces (substantial investment by academic institutions into upstream research, availability of the complete sequence of the *P. falciparum* genome, among others), was insufficient to foster the establishment of a credible product pipeline. The recent creation of two dedicated initiatives to drive malaria vaccine R&D, both in Europe (European Malaria Vaccine Initiative - EMVI) and in the USA (Malaria Vaccine Initiative - MVI) has provided an additional element in the form of Management and Funding push. The previously modest pull forces have also been reinforced. The Malaria R&D Alliance intends to increase the level of advocacy for malaria interventions, and USAID and MVI have conducted a study in Africa to assess the future market for a malaria vaccine. It is hoped that a clearer definition of the demand (market pull) for such products will stimulate industry investment into this area and accelerate discussion within Ministries of Health on strategies to introduce such a prevention tool (health priority pull). Finally, the malaria vaccine R&PD community has recently embarked upon an exercise referred to as “Technology Road-mapping”. Used mainly by industry to define new pathways for innovation and increased efficiency, technology road-mapping intends to accelerate and improve the development of promising malaria vaccines by providing a cohesive framework for defining critical needs and focusing technology investments, producing a blueprint to align and guide activities within the global malaria community, catalyzing new investment and focusing donor funds on highest priority needs.

In addition to these promising efforts concentrating on malaria vaccines, several recent investments into dedicated R&D funding, technologies and management in the form of not-for-profit "enterprises"[9,10,11] similarly bring hope for a breakthrough in the area of HIV and tuberculosis vaccine R&D, among others.

As elaborated earlier, all these driving forces are instrumental in ensuring that enough vaccine candidates are moved through the R&PD process to make certain that one or more effective products will eventually be licensed and introduced into immunization programmes. Following this line of reasoning, the concept of a global vaccine R&PD portfolio pipeline emerges, summarizing all the individual efforts and initiatives for researching and developing vaccines targeting infectious diseases of public health importance.

A Global vaccine R&PD pipeline already exists

The various vaccine R&PD stages include discovery, preclinical research, clinical/regulatory and post-licensing research. In parallel with these, work on future access to vaccines should be undertaken early for all infectious diseases of public health importance in developing countries. In order to increase both the efficiency and probability of success of the outcomes of individual vaccine-related initiatives, the work of all partners should be viewed as being component elements of a concerted, global effort. In this manner, while respecting the integrity of the individual entities contributing, an informally integrated emerging, common Global Pipeline can be derived. Using this approach the global R&PD pipeline focussing on WHO priority vaccine is schematically assembled below (see Figure 3):

Vaccine R&PD is a high-risk undertaking. Viewed statistically, the Global product "pipeline" requires many early stage development projects to generate one successful product: the probability for a pre-clinical vaccine candidate reaching the market has been estimated at 0.22 i.e. odds of around 5 to 1 against success. As a result, to register a single vaccine there need to be 4 to 5 independent vaccine candidates under development.[5] The uncertainty of research outcomes makes establishing and maintaining such a pipeline a necessity. To ensure the likelihood that a vaccine will actually emerge on the market, the pipeline must be composed of an R&PD portfolio of different vaccine candidates in different stages of development for each of the targeted diseases, as well as activities assuring future accelerated introduction and access.

Certain gaps can be identified in the current Global Vaccine pipeline. For example, for leishmania only one recombinant vaccine candidate (supported by IDRI) has entered clinical trials in USA and Latin-America; in the case of malaria, many vaccine candidates concentrate on the same parasite proteins, potentially repeating similar trial results while neglecting novel target opportunities; for bacterial pneumonia, the current vaccines do not cover all disease serotypes required in developing countries and new vaccine candidates would need substantial investment to reach the market; for HPV and cervical cancer, the issues of access for adolescent girls in poor countries have not been addressed enough in advance and vaccines will be licensed in 2006 without sufficient data to promote their effective introduction in developing countries. In

addition, the importance of carrying out research in true partnership with developing countries should not be under-emphasized. For the Global pipeline to efficiently operate and keep delivering optimal vaccines for resource-poor countries, the coordinated efforts of all partners should be employed to strengthen research, product development, as well as regulatory, ethical evaluation and post-marketing surveillance. Moreover, the participation of developing countries in setting research scope and priorities, and in defining required target product profiles for new vaccines is essential for future success of vaccine development and implementation.

Even when efficient vaccines are developed and introduced, R&PD can not then cease. Implementation research, post-marketing surveillance, bridging studies enabling optimal target population and immunization impact evaluation, among others, are all necessary and vital components of successful vaccine introduction and roll out. Collectively, these post-approval activities ensure the maximization of a vaccine's life saving impact. Akin to the life-cycle management approaches applied to commercial vaccines, innovation and research focused upon the provision both of better vaccines and enhanced vaccine delivery systems should also continue as well as approaches to improve manufacturing process to continually reduce vaccine unit cost to the end-user. In short, the existence of an "ever-green" vaccine pipeline, constantly delivering new or improved products to the market is critical.

In summary, despite positive trends (as discussed above) the current level of investment into building sustainable R&PD driving forces has not yet reached a sufficient level. The apparently complex Global Pipeline does not cover all essential aspects of the vaccine development continuum. It suffers from many gaps, and is still insufficiently deep to deliver successfully some of the essential vaccines. In addition, participation of developing countries research and diseases control entities in the process is often underweighted.

In order to meet the challenges of the MDGs, a new coordinated vaccine R&PD paradigm needs to be built with the active participation of all stakeholders. On the back-drop of this convergence of efforts and acting as a cornerstone to the increased coordination, countries in the developing world should play a central role in identifying and communicating the specific vaccine products they need. WHO will play a critical role in ensuring that this occurs.

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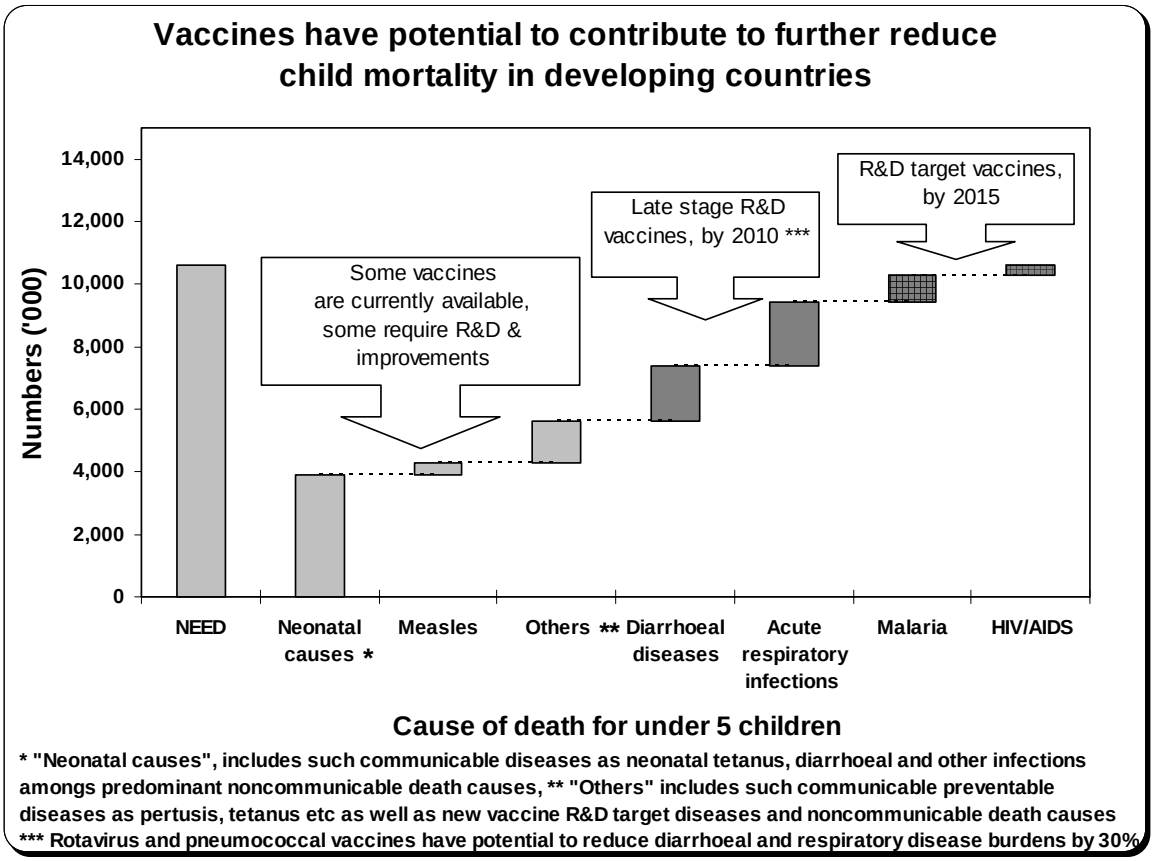
Legend to Figure 3

ADIP- Accelerated Development and Introduction Plan; Aeras - Aeras Global TB Vaccine Foundation; ANRS- Agence Nationale de Recherches sur le Sida, France ; ARIs-Acute respiratory infections; ARC – Amercian Red Cross, CIDA- Canadian International Development Agency (Canada); CDC- Centers for Disease Control, USA; CVD- Center for Vaccine Development, USA; CVP- Children's Vaccine Program at PATH; DFID- UK Department for International Development; EMVI-European Malaria Vaccine Initiative; ETEC- Enterotoxigenic *Escherichia coli*; EU- European Union (funded projects), Hib-*Haemophilus influenzae* type b; HIV- human immunodeficiency virus; HPV- human papillomavirus; HSV- herpes simplex virus; HVI-Joint WHO-UNAIDS HIV Vaccine Initiative; GBUI- Global Buruli Ulcer Initiative, IAVI- International AIDS Vaccine Initiative; IDRI-Infectious Disease Research Institute; IVI-International Vaccine Institute; IVR-WHO Initiative for Vaccine Research; MRC-Medical Research Council, UK; MVI-Malaria Vaccine Initiative at PATH; MVP- Meningitis Vaccine Project; NCI-National Cancer Institute, NHMRC-National Health and Medical Research Council; NIH-National Institutes for Health, USA; SIDA- the Swedish International Development Cooperation Agency; PATH-Program for Appropriate Technologies in Health; PDVI-Paediatric Dengue Vaccine Initiative; TDR-UNICEF-UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Disease; UNDP- United Nations Development Program; USAID- United States Agency for International Development; USDA-U.S. Department of Agriculture; WRAIR-Walter Reed Army Institute of Research.
Note: Although this review focuses on international and national entities supporting global vaccine research initiatives, it is of note that the private sector and developing country institutions also greatly contribute to the global pipeline.

Figure 1. Vaccine contribution to reduce child mortality



*** "Neonatal causes", includes such communicable diseases as neonatal tetanus, diarrhoeal and other infections amongs predominant noncommunicable death causes, ** "Others" includes such communicable preventable diseases as pertusis, tetanus etc as well as new vaccine R&D target diseases and noncommunicable death causes**
***** Rotavirus and pneumococcal vaccines have potential to reduce diarrhoeal and respiratory disease burdens by 30%**

Fig. 2 Driving forces for public health research and product development

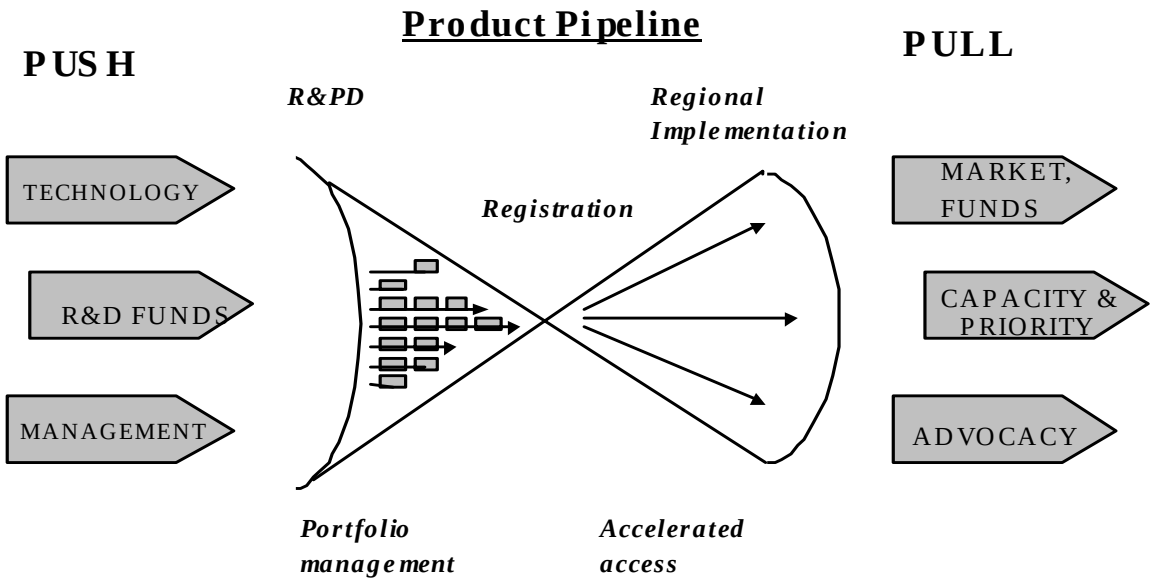
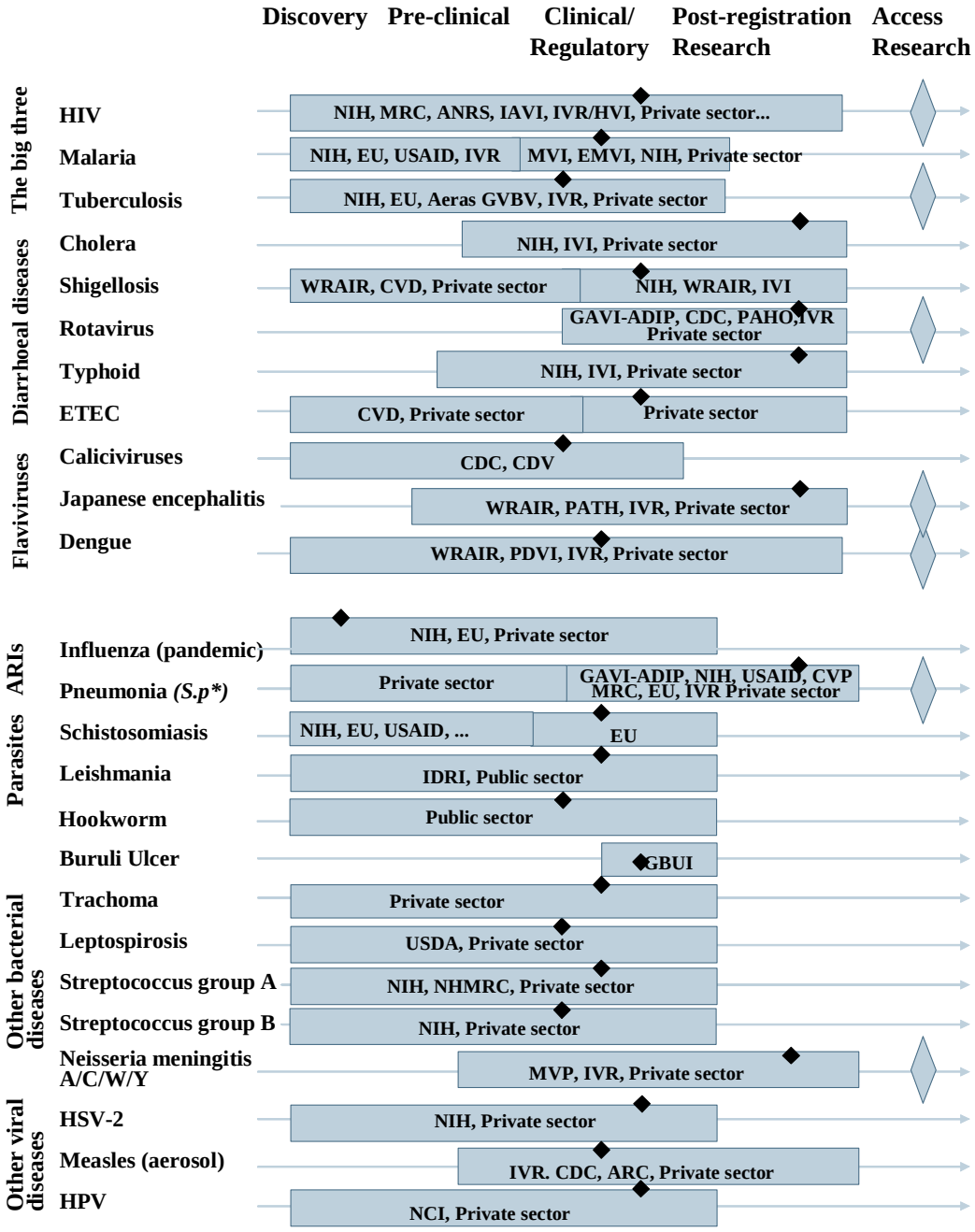


Figure 3

Global vaccine R&D pipeline

Partners promoting vaccine development against diseases of developing world



Notes

- *The black diamond indicates the stage of the most advanced candidate*
- *In this diagrams only international players are acknowledged with appreciation of extensive work performed by national developing countries institutions*