

## **NOVEL APPROACHES FOR THE DESIGN OF VACCINES AGAINST INFECTIOUS AND AUTOIMMUNE DISEASES**

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The renaissance in vaccine research during the past decade led to several new approaches towards vaccine development. One is the evaluation of the potential of synthetic peptides corresponding to sequences of microbial proteins, comprising defined epitopes, to elicit antibodies with capacity to inactivate the respective pathogens and to protect against infection. Focusing on influenza, a novel approach – synthetic recombinant vaccines – was developed, in which the relevant epitopes are expressed by genetic engineering. Oligonucleotides coding for three influenza epitopes stimulating B cells, T helper cells and cytotoxic T lymphocytes (CTLs), respectively, were individually inserted into the flagellin gene of a *Salmonella* vaccine strain. The protective immunity, even against a lethal challenge, conferred by a vaccine, comprising a mixture of these three constructs, persisted for at least seven months and was effective against several strains of influenza. These results are indicative of the potential of such synthetic constructs as a long-range and broad-spectrum vaccines against influenza in other viruses, including HIV. A similar approach led also to protective immunization against the parasite *Schistosoma mansoni*.

In contrast to infectious diseases, where the goal of a vaccine is preventive, by increasing the immune response of the host against the specific pathogen, in the case of autoimmune disorders it is desirable to decrease the response to the epitope(s) leading to the damage, without otherwise interfering with the immune response of the individual. We have focused on the inflammatory demyelinating disease, multiple sclerosis and its animal model EAE. A protein-like polymer, denoted Copolymer 1, which is immunologically cross-reactive with the major myelin component Myelin Basic Protein, was shown to exert a specific suppressive effect in exactly that manner. After finding that it suppresses very efficiently the animal model in several species including primates, its beneficial effect in MS patients was demonstrated in several clinical trials (Phases I, II and III), with an excellent safety profile. As a result, this copolymer was developed into a drug, COPAXONE®, which was approved for the treatment of MS patients in many countries worldwide. This introduces a novel concept – an antigen-specific vaccine/drug against an autoimmune disease. Furthermore, this is within the realm of a broader aspect, namely the development of therapeutic vaccines.

## CHIMERIVAX TECHNOLOGY SUCCESS WITH A WEST NILE VACCINE DEVELOPMENT AND OTHER PROMISING INDUSTRY-DRIVEN TECHNOLOGY PLATFORMS

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Existing platform technologies are keys to the success rate needed when developing fast-track programs to evaluate vaccines or immunotherapy approaches. Therion Biologics has developed a set of pox virus vectors that have an established safety profile in humans and can simultaneously express multiple antigens, co-stimulatory molecules, and immune-modulating proteins. These vectors have proven safety and tolerability and are efficient in manufacturing processes. AlphaVax developed a unique system to produce "replicon particles" creating safe promising vaccines against alphaviruses (e.g., Venezuelan Equine Encephalitis). The platform has also been used to vaccinate against heterologous antigens such as influenza, Lassa fever, Ebola and Marburg. Acambis ChimeriVax technology employed 17D vaccine strain of yellow fever (YF) virus to produce a chimeric live virus containing the capsid and nonstructural genes of YF and the envelope genes (prME) of West Nile (WN NY99) virus. This approach was previously used to produce YF/Japanese encephalitis and dengue vaccines that are in clinical trials. The YF/WN chimera containing wild-type (*wt*) prME protein did not cause encephalitis in young mice after peripheral inoculation in contrast to the parent WN NY99 strain. Point mutations at defined sites of the E protein (designated F, V, and R) effectively reduced the neurovirulence of the YF/WN<sub>wt</sub> chimera. In a variety of animal models, including mice, hamsters, horses, and monkeys the vaccine has been shown to be safe and immunogenic and/or protective. Rhesus monkeys vaccinated with a single dose of vaccine constructs containing single <sub>F</sub>, double <sub>VR</sub>, or triple <sub>FVR</sub> mutations developed viremias similar to YF-VAX® in duration but significantly lower in magnitude. The lower viscerotropism (viremia) supports the safety profile of the vaccine constructs. ChimeriVax-WN vaccinated rhesus showed fast seroconversion and no clinical signs were noted after challenge. ChimeriVax-WN is a promising single dose, safe and protective live attenuated vaccine against West Nile.

## **MITIGATING THE IMPACT OF HIV/AIDS ON THE EDUCATION SECTOR IN AFRICA: THE MANAGEMENT CHALLENGE**

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HIV/AIDS in the developing world is not simply a health issue, but the single most important *management* issue confronting the sustainability and development of public systems such as education. As matters stand it will impact every aspect of education system management, teaching and learning for decades to come, *even* if a vaccine was to be developed and introduced tomorrow. For example, in one education system enrolling almost 3 million pupils, enrolment in Grade 1 was 24% smaller in 2001 than it had been in 1998, suggesting major impact on output 12 to 16 years on. In the same system, 80% of teachers will have to be replaced by 2010 due to 'normal' attrition being inflated by AIDS. It should be noted that the primary impact of HIV/ AIDS on public systems is to explode the scale of *existing* systemic dysfunction and management problems. In the case of education this highlights issues of labour, enrolment and gender, orphaning, school fee decline, transition rates and system output, and geographic variation of impact. Thus good system management may be said to hold the key to HIV/AIDS mitigation, system sustainability and effective prevention and care. To be viable, this requires the regular collection and analysis of data on system input, function and output required to provide a management information/decision support system and generate an HIV/AIDS impact 'early warning system'.

This approach is being taken in several high-incidence African countries by the HEARD-based and USAID-funded Mobile Task Team on impact in the education sector, with promising results. The approach is linked to the 'opportunity' inherent in a crisis of this magnitude, to initiate long-overdue reform and redesign measures designed to make education delivery more effective and cost-efficient. A related team is now piloting a similar systemic management approach in a number of SSA health departments and a multi-sectoral approach to identifying and managing growing numbers of orphans using GIS is being tested.

## **DEVELOPING AND ADAPTING NEW TECHNOLOGY TO LOCAL NEEDS : CHALLENGES IN DEVELOPING COUNTRIES**

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Many of infectious diseases are the public health problem in Thailand. Emerging or re-emerging infection like HIV, *M. tuberculosis*, Dengue virus and *Leptospira* are yearly epidemic. From the report of Division of Epidemiology, Ministry of Public Health, Thailand, HIV infected persons are recently about 800,000 cases with 140,000 cases of AIDS patients and more tendency in HIV pediatric cases. In parallel, the opportunistic infection of TB is increasing and latent TB infection with unknown evidence is estimated more than 20,000 cases per year. By the reason, Thailand needs urgently drugs for procurement AIDS and TB patients, the efficacies of HIV/AIDS and BCG vaccines and also especially diagnostic tools for monitoring of drug resistant or identification of latent TB or other infections from the vaccinated ones. Thailand is one of the countries that locally produce drug against HIV infection and progressing on HIV/AIDS vaccine trials for subtype E specific epidemic in our country.

In case of the tropical countries like Thailand, they are endemic area of Dengue Haemorrhagic Fever (DHF) and Leptospirosis. In each year more than 60,000 and 11,000 cases with the mortality rate 0.13% and 5-10% are for DHF and Leptospirosis, respectively. Therefore, it urgently needs for vaccines against these diseases.

From the consideration, different diseases or at least different subtypes or strains occurred in different regions in the world. Each country should establish its own capability on research and development for production of diagnosis, drugs and vaccines under the national or international collaboration for more effectiveness. Modern Biotechnology such as Genomics and Bioinformatics etc. is nowadays essential development of effective tools for diagnosis, drugs and vaccines for advance control and treatment of infectious diseases.

## NEW AND UNEXPECTED DISEASES IN OECD COUNTRIES: ANTICIPATING THE RISKS

**PETER BORRIELLO**

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New and emerging/re-emerging infections have received much recent interest and publicity. Scientific and public health interest has been sufficient to sustain a peer-reviewed journal dedicated to the subject (Emerging Infectious Diseases). The definitions however are applied loosely. This presentation will propose a series of 'sub-category' definitions and give examples within each. The proposed categories are:

1. A new infection based on emergence since 1970, *e.g.*, HIV.
2. A long-established disease where the aetiological agent has only recently been discovered, *e.g.* Whipples disease.
3. Recognition that a presumed single species of pathogen consists of different species with possible differing pathogenic mechanisms *e.g.*, cryptosporidia.
4. Old diseases in new presentations and population groups due to changes in behaviour, *e.g.* botulism in injecting drug abusers, or environments *e.g.*, iatrogenic *Clostridium perfringens* diarrhoea in hospitalised elderly patients.
5. Infections in individuals and populations due to changes in host susceptibility, *e.g.*, infections in AIDs patients.
6. Re-emergence due to compromise of effective preventative measures such as reductions in vaccine cover, *e.g.*, diphtheria.

This sub-categorisation will help better to anticipate the risks.

## **OLD ENEMY-NEW TOOLS: THE FIGHT AGAINST TRYPANOSOMIASIS**

**KARIN BRÜNING**

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The Brazilian experience to control American Trypanosomiasis was based upon intensive efforts to eliminate the vector of the disease. Some statistics demonstrating the success of this strategy will be presented. Another way to fight most of the neglected diseases using low budgets has been the development of new drugs, derived from the already existing ones, in order to decrease their toxicity and maintain the activity. Our experience with a drug against African Trypanosomiasis will also be reported. The last and most important step in the “stream-line” of technological development is the product to reach the consumer. Unfortunately, in most of the countries where Trypanosomiasis is still an “old enemy” a considerable part of the population does not have free access to medical care. In this sense, the Brazilian Health Programms have shown an alternative way to guarantee the treatment of most endemic diseases.

## PERSPECTIVES FROM THE COMMISSION FOR MACROECONOMICS AND HEALTH

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The Commission on Macroeconomics and Health (CMH) was established in January 2000 to assess the place of health in global economic development. The Commission's report, produced by 18 of the world's leading economists, public health experts, development professionals provides compelling evidence that better health for the world's poor is not only an important goal in its own right, but can act as a major catalyst for economic development and poverty reduction.

Since the CMH Report was launched in December 2001 it has a major impact internationally, notably at the *International Conference on Financing for Development* where the need for increased spending on health was a prominent theme throughout the debate. The report was also central to WHO's contribution to the *World Conference on Sustainable Development* in Johannesburg. Several countries around the world are currently beginning to act on the recommendations of the report with support from WHO and other partners.

The key message of the CMH is that the resources and know-how exist to save millions of lives. To do so, however, will require a new "health pact" between governments and development agencies, in which both parties make significant increases in their allocation of resources for health. The bulk of these resources will focus on scaling up activities to improve health outcomes in developing countries. However, to sustain the effectiveness of these activities over the long-term will require a) concomitant increases in the level of funding invested in the development of new drugs, vaccines and diagnostics, b) more focused attention on the means through which these resources are mobilized, managed and disbursed, and c) greater coherence in the international policies and trade agreements which influence peoples' access to key health technologies - notably pharmaceuticals.

## ANTIBIOTIC AND DRUG RESISTANCE

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The development of bacterial resistance, including multidrug resistance, is inevitable because it represents a particular facet of the general evolution of bacteria. Resistance to antibiotics can result from mutations in structural or regulatory house keeping genes that are passed vertically from one generation to the next. Alternatively, it may result from horizontal acquisition of foreign genetic information from bacteria of the same genus or from different genera. The two phenomena are not mutually exclusive and together may result in the emergence and more efficient dissemination of resistance. Bacteria are particularly adept at gathering resistance genes, whether isolated or grouped in operons, that mediate resistance to antimicrobials. The combination of various biochemical mechanisms against the same class of antibiotic confers high levels of resistance to the bacterial host. Association of genetic structures ensures stability and vertical inheritance as well as horizontal spread of antibiotic resistance genes in phylogenetically remote bacteria genera. In addition to this « quantitative » aspect of resistance, a major finding was the discovery of the « qualitative » broad spectrum of certain resistance mechanisms or combinations thereof. The concept that resistance is a class phenomenon recently lost favor because of the extension of the concept of cross-resistance and the increased occurrence of co-resistance. In classical cross-resistance, a single biochemical mechanism confers, resistance to a single class of drugs: use of a given antibiotic can select resistance to other members of the group but not to drugs belonging to other classes. However, cross-resistance between drug classes can occur by two mechanisms : overlapping targets and drug efflux. Active efflux of the drugs outside bacteria has been recognized as a very common resistance mechanism. This energy dependent export confers low-level resistance to a wide variety of antibiotics. The broad substrate specificities of the pumps account for decreased susceptibility to  $\beta$ -lactams, aminoglycosides, tetracyclines, chloramphenicol, trimethoprim, sulfonamides, fluoroquinolones, and macrolide-lincosamide-streptogramin antibiotics, among others. In contrast to cross-resistance, co-resistance is due to the presence, in the same host, of several mechanisms, each conferring resistance to a given class of drugs. In addition, the corresponding genes are often adjacent (physically linked) and expressed in a coordinated fashion. One of the most efficient system of this type is represented by the integrons first described in Gram-negative bacilli and more recently found in Gram-positive bacteria. Because of the genetic organization resulting in co-expression of the various genes, use of any antibiotic that is a substrate for one of the resistance mechanism will co-select for resistance to the others and thus for maintenance of the entire gene set. It thus appears that bacterial genetic tinkering can lead to resistance to every antimicrobial agent.

## **UNDERSTANDING THE CHANGING PATTERN OF INFECTIOUS DISEASES**

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The microbial world is complex, dynamic, and constantly evolving. Several recent trends have accelerated this natural propensity to change, resulting in the emergence of new diseases at an unprecedented rate, a dramatic resurgence of several epidemic-prone diseases, and the rapid evolution of antimicrobial resistance. These trends have also encouraged easier travel of micro-organisms around the globe in humans, insects, food and livestock. The result is a rapidly and sometimes dramatically changing global infectious disease situation. Cholera is in its seventh pandemic. Yellow fever is poised to cause urban epidemics. The 1998 epidemics of dengue and dengue haemorrhagic fever were unprecedented in numbers of cases and deaths, and the epidemics of 2002 have already seen even higher numbers of cases. A new strain of epidemic meningitis, W135, emerged in 2002, defying emergency preparedness in the form of stockpiled vaccines against conventional strains. And the identification of AIDS in the early 1980s has led to high levels of mortality and changing demographic patterns in sub-Saharan Africa. At the same time the return of TB as a global threat has been accompanied by the emergence of multidrug-resistant forms costing up to 100 times more to treat. Malaria may soon be resistant to all currently available first-line drugs. Drug resistance to common bacterial infections is now pervasive. These changes create a constant and urgent need for new drugs and vaccines. The Roll Back Malaria and Stop TB partnerships are examples of a new type of partnership building sustainable control of these two diseases, reinforced by the Global Fund on AIDS, TB and Malaria that gives countries resources to procure and use drugs against these diseases. The Medicines for Malaria Venture, the Global Alliance for TB Drug Development and the Initiative for Vaccine Research are other public-private partnerships that ensure the research and development to bring badly needed yet unprofitable drugs and vaccines to market using the same technologies applied in industry-run discovery projects.

## RESURGENT DISEASES IN OECD COUNTRIES

SVEN HOFFNER,

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There are today over 1400 microbes identified as potential human pathogens. Most are bacteria (538 species) followed by fungi, viruses and other etiological agents. A clear majority of them are almost totally unknown in the OECD countries, and in fact of no or very limited public health significance, at least in our part of the world.

However some are neglected causes of disease and a few constitute real threats to human health and well being. They might have the capacity to give rise to outbreaks of disease e.g. *Corynebacterium diphtheria*, the causative agent of diphtheria, or to cause slowly increasing endemics, such as *Mycobacterium tuberculosis* (TB). I will focus my presentation on the later – the bacteria referred to as “The captain of these men of death”, an agent that claims some 2.5 million lives globally every year.

During the last decade two factors have made the tuberculosis problem much more difficult to control. Firstly, the increasing numbers of HIV-infected individuals, who are at a significantly increased risk of developing active TB, and thus responsible for increased spread of this disease, also to the HIV-negative population. Secondly, the increased prevalence of resistant – and multidrug resistant (MDR) – forms of the disease, making the standard chemotherapy less effective and the patients infectious over very prolonged periods. The incidence of TB in most OECD countries is low, ranging from around 5/100.000 in e.g. USA, Italy, Norway and Sweden up to 47/100.000 in Korea. However, microbes do not respect any national borders and MDR-TB is prevalent in our neighborhood, such as countries of the former Soviet Union. Thus we need to increase our awareness and prepare for a possible, and unfortunately likely, increase of drug resistant TB also in many of our countries. Such an increase has already been observed in e.g. Germany, Denmark and Sweden.

## **THE ROLE OF ORPHAN DRUG LAWS AS INCENTIVES FOR THE R&D OF NEGLECTED DISEASES**

**KENNETH I KAITIN**

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This presentation will review the provisions of the US Orphan Drug Act (ODA) and examine how it serves as an incentive for research and development on treatments for rare diseases. The therapeutic areas, product types, sponsor characteristics, and market factors that are most compatible with orphan product development will be discussed. In addition, the history of the ODA as a mechanism for encouraging the approval of medicines for neglected diseases will be explored. The presentation will conclude with a discussion on how modifications to the ODA may enhance its utility for incentivizing R&D on treatments for neglected diseases.

## **PUSH-PULL INCENTIVES TO MOTIVATE PRIVATE INVESTMENT INTO NEGLECTED DISEASE PRODUCT R&D**

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In 2000, more than 10 million people died from malaria, tuberculosis, HIV and diarrhoeal diseases. The majority of these deaths took place in the poorest regions of the developing world.

A combination factors, including hurdles to accessing existing products and the absence of effective treatments, account for the persistence of parasitic and infectious disease cases in the developing world. R&D into new interventions – drugs, vaccines, diagnostics – is a critical component of a broader solution package to address these problems.

Private industry – biotechnology and pharmaceutical companies - plays a fundamental role in the discovery and development of new interventions. The neglected diseases of the poor have tended to be a relatively low R&D priority because of the significant scientific challenges and poor expected returns on investments in these diseases. Explicit policy interventions are required to motivate increased company involvement.

One approach is for governments with important R&D based pharmaceutical industries, especially the US, EU, and Japan, to introduce a package of incentives, similar in concept to the existing orphan drug legislation, that enhance the attractiveness of investing in neglected disease R&D projects. This package must combine push incentives that reduce the up-front costs of R&D and pull incentives that increase the expected return on investment for companies who bare the risks.

Incentive packages should complement rather than substitute for the focused, managed, R&D public private partnerships. The key advantage of incentives is, if effective, they will bring into the “global health R&D space” company funded and managed projects. The key disadvantages are they are difficult to implement (depend on assertive and coordinated government action) and there are no guarantees that companies will respond once the incentives are introduced.

## **INFECTIOUS DISEASES IN THE ERA OF GLOBALISATION**

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Health is an essential component of sustainable development and infectious diseases and constitutes a major part of the health burden which developing countries face. Almost 95% of the 17 millions of yearly deaths caused in the entire world of infectious agents occur in developing countries. Hundreds of millions of people suffer from severe, debilitating diseases (AIDS, malaria and others), the economical impact of which is huge. Infectious diseases “travel” more than ever, and epidemics can spread fast. Bioterrorism and biological weapons add another dark touch to the picture.

Two examples will be used to analyse the current, unacceptable situation and identify the weak or missing links : the spreading of meningitis in Africa, and the lagging development of an AIDS vaccine. Both cases show how a combination of scientific, technical, regulatory and political factors contribute to generate a situation which is a root cause of major health disasters. In the more general framework of neglected diseases, the emergence of new initiatives, such as GAVI or DNDi, constitutes major positive steps which, unfortunately, cannot, by far, answer to all urgent needs.

## **PROTECTION: SURVEILLANCE AND DIAGNOSIS**

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Surveillance – the systematic collection, analysis, and interpretation of clinical, laboratory or other data – provides indispensable information for public health actions. The principles of public health surveillance are well established, but the changing patterns of infectious diseases, advances in diagnostic tools and informatics give rise to changes in the scope of and the approach to communicable disease surveillance.

Public policies should focus on an integrated approach to surveillance to optimize disease control and international cooperation, including information and knowledge transfer. International research agendas, *e.g.*, within the EU or OECD, should adequately support the needs of public health. This requires that relevant public health research questions are formulated by the public health community and included into the research agenda. The international coordination of surveillance activities will help providing the necessary information needed to better protect our population against infectious diseases.

## REVERSING THE TREND OF EMERGENT/RESURGENT VECTOR-BORNE DISEASES

VICENTE LARRAGA

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The development and widespread use of vaccines against infectious diseases has been one of the great achievements of medical science. The currently available vaccines are able to induce long-lived antibody responses which are the main agents of immune protection against most bacteria and viruses. However, vaccines against intracellular organisms that require a cell-mediated immune response such tuberculosis, malaria, leishmaniasis, Chagas disease, sleeping sickness or AIDS are not available or not highly effective. Considering the morbidity and mortality associated with these diseases the development of vaccines able to trigger cellular responses is important. A new form of vaccination based on DNA containing genes encoding for reactive antigens able to generate humoral and mainly cellular responses is being investigated. We are going to present, as an example, the development of a recombinant DNA vaccine encoding for a *Leishmania* antigen (LACK) in an heterologous vaccination regime, able to induce protection in dogs, the main reservoir of the parasite both in the Old and New worlds. Leishmaniasis affects fifteen million people worldwide with two millions of new cases a year and three hundred fifty million people at risk. It has been declared as emergent disease in Europe by its association with AIDS.

## **MONITORING RESOURCE FLOWS FOR HEALTH R&D ON NEGLECTED DISEASES: WHAT DO WE KNOW AND WHAT NEEDS TO BE DONE?**

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The WHO Ad Hoc Committee on Health Research Relating to Future Intervention Options concluded that the international health community has failed to allocate R&D resources rationally to the most debilitating global health problems. It is therefore essential to monitor financial flows for health R&D on persisting major health problems, and identify gaps in the allocation of financial resources that have the greatest potential to yield the knowledge and tools (diagnostics, drugs and vaccines) needed to reduce the share of burden that cannot be avoided with existing tools. Unfortunately shortcomings in the available data do not allow us to do so.

Infectious diseases mostly prevalent in low-income and middle-income countries have been neglected even though they represent half of the global burden of disease in Sub-Saharan Africa and forty five percent in other regions where child and adult mortality are high. HIV/AIDS, malaria, acute lower respiratory infections, vaccine preventable childhood diseases and diarrhoeal diseases are the five largest causes of burden in SSA. Investments on R&D for these diseases have been woefully inadequate in the past. The recent political commitment to increase investments to reduce the burden of HIV/AIDS, malaria, and tuberculosis, coupled with recent advances in biotechnology offer a promising opportunity to make a significant difference.

Much work lies ahead to reduce the fragmentation of available data, increase international data comparability, and reach an agreement on the framework for this analysis. The success of this undertaking requires strong political will from major funding partners in all sectors to participate in this effort.

## **INTERNATIONAL NETWORK FOR THE CONTINUOUS DEMOGRAPHIC EVALUATION OF POPULATIONS AND THEIR HEALTH IN DEVELOPING COUNTRIES (INDEPTH)**

**HASSAN MSHINDA**

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Traditional sources of health information collected from health facilities often serve as the basis for understanding health problems, planning for health services and allocation of resources. However, not all sick individuals access formal health services because of geographical, social and economic reasons, as a result the information generated from formal health services is fragmentary and biased. This void of health information for a large populations in developing countries makes it difficult for policy makers to formulate rational health policies.

INDEPTH is the network of 29 health and evaluation sites in Africa and Asia, which collects community based health information, accurately reflects the prevailing disease burden of populations; assist in monitoring new health threats, such as emerging and reemerging infectious diseases and drug resistance; platform of action oriented research to test and evaluate health interventions, such as a new vaccines or drugs.

Biotechnology tools have been applied mainly as a molecular epidemiology tools for microbial diversity and drug resistance. The paper highlights the potentials and challenges of using biotechnology tools in developing countries.

## MODELLING EPIDEMIC SPREAD AND COUNTERMEASURE: A TOOL TO ASSIST PUBLIC HEALTH PLANNING AND RESPONSE

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An effective response to any emergency usually depends on swift, well rehearsed actions based on prior planning. In some cases of spread of infectious disease (for example new or reemerging pathogens, or deliberate release) there is (fortunately) a lack of real experience on which to base appropriate emergency response plans. Mathematical (computer based) modelling provides a potentially powerful tool to simulate possible events and assess the likely impact of alternate courses of action. The use of modelling methods as the basis for decision making is well accepted across a range of industries including engineering, power supply & distribution, economics & meteorology. In infectious diseases such methods have been used extensively to model impact of vaccination, and the results have helped to determine national immunisation programmes. Its use in emergency planning for infectious diseases is a more recent development.

The utility of this approach, and the associated issues, will be illustrated with three examples. The first of these is directly relevant to the subject of bioterrorism (smallpox: Gani & Leach 2001, *Nature* **414**: 748), the others provide an example of spatial modelling (measles epidemics in the UK: Grenfell BT *et al.* 2001, *Nature* **414**: 716.), and of real time modelling to guide emergency responses (the foot and mouth epidemic in the UK: Ferguson *et al.* 2001 *Science* **292**: 1155.).

In preparing to counter the effects of bioterrorism, the importance of awareness and detection is now influencing education and communication programmes, and these methods have been used to give guidance on antibiotics and vaccine requirements. Perhaps most importantly, these tools provide an evidence basis for decision making.

**PERPSECTIVES ON A EU WIDE STRATEGY TO STIMULATE R&D  
ON NEGLECTED DISEASES**

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An EU wide strategy cannot rest on pro-active elements of research policy alone but needs to develop synergistic actions between policies in trade, research and development cooperation policies, in particular capacity building strategies for clinical development. There is no questioning of the benefit to substantially increase public funding for neglected diseases, but the validity of funding instruments and regulatory facilitations need to be re-assessed. Moreover, a systematic and permanent review of R&D support mechanisms needed to not only guarantee R&D outcomes, but also accelerate widespread availability of new global public health goods for neglected diseases is to be considered

On the other hand , the European Treaty provides a basis for joint action between the Community and its Members States in order to bring on board all the resources necessary both scientifically and materially. A third strategic element is constituted by the EU/ACP development partnership; The synergistic use of these unique elements will be explained

## **TECHNOLOGICAL OPPORTUNITIES AND ECONOMIC PROBLEMS OF VACCINE DEVELOPMENT. THE EXAMPLE OF REVERSE VACCINOLOGY.**

**RINO RAPPUOLI**

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Since the discovery that microbes cause infectious diseases and that vaccination can be used to prevent them, the first task of every scientist working in vaccine development has been to grow the infectious agent. The *in vitro* grown microorganisms then could be used as starting material for the identification of protective antigens or could be manipulated, usually by multiple *in vitro* passages, in order to obtain a live-attenuated microorganism.

The DNA sequence of the whole genomes of microorganisms allowed for the first time to tackle vaccine development starting from the computer prediction of protective antigens and to obtain vaccine candidates without the need of growing microorganisms. In order to underline the different path to vaccine discovery that has been made possible by the genomic sequencing, this new method has been named "reverse vaccinology".

Reverse vaccinology is not just a different method to practice vaccine development, but it is a powerful tool to tackle those vaccines that have been difficult or impossible so far. The first example of a genome-based vaccine development has been serogroup B meningococcus. In this case, forty years of vaccine research using the conventional approaches had discovered 15-20 potential antigens, which unfortunately had been ineffective in providing a vaccine that could universally protect against the disease. The availability of the genomic sequence made available at once all potential antigens encoded by the bacterium. 600 novel potential antigens were identified by computer prediction, expressed as recombinant proteins in *Escherichia coli* and tested as vaccines within 18 months. 29 novel antigens were found to be good vaccine candidates. The best among the novel antigens have been used in subsequent studies to design an universal vaccine to be tested in clinical trials. The same approach used for meningococcus B is now being applied to several microorganisms and is likely to lead to the development of many novel vaccines.

In conclusion, the present is one of the best moments in history for vaccine development . The information provided by the genomic era has made available in databases all possible antigens of nearly all pathogenic microorganisms. The progress in immunology and vaccine delivery is making possible to target all arms of the immune system. GAVI and the vaccine fund are making available an unprecedented amount of money.

Nevertheless, vaccines are not a priority for industry and this may jeopardize the future of vaccines unless properly addressed on a global basis

## **DEALING WITH SHORTAGES: FACILITATING DEVELOPMENT, PRODUCTION AND PROCUREMENT OF EXISTING AND NEW VACCINES**

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Vaccines are biological products and are therefore vulnerable to unpredicted problems during manufacture – that may not become apparent until manufacturing is complete, and they are also vulnerable to environmental effects during delivery and storage. Production of vaccines is time and volume restricted according to their manufacturing process. The requirements for compliance with Good Manufacturing Practice have progressively increased also. These factors alone make for supply uncertainties, and prevent rapid responses to changes in demand. For example, it can take almost three years from start-up to market readiness for polio vaccine: if demand changes during that time, there can either be surplus or shortage.

In recent years, there have been shortages of routine vaccines that had been in regular production for many years, affecting industrialised and developing countries. Such shortages can be enormously disruptive to routine or supplementary activities.

On the consumer end, uncertainties over continuity of supplies encourages over-ordering, and leads inevitably to wastage – because of the sometimes short shelf-life of these products. In the case of new vaccines, much can be done to coordinate national plans for their introduction with the tasks of manufacturers who will supply the product. Although the target group may be identifiable in advance, the pace at which vaccine may be used may either exceed demand, leading to shortages, or be over-estimated, leading to wastage. In 1999, the UK introduced a new vaccine for which there was huge public interest, but supplies were restricted to the speed at which the vaccine could be manufactured. The campaign was managed by matching demand tightly against supply with restricted allocation of vaccine only to those according to epidemiological risk. The model of ‘allocation supply’, instead of ‘demand ordering’, is now regularly used to smooth out the ebbs and flows of supply, minimising shortages.

## **THE ADVANCED TECHNOLOGY PROGRAM: PROMOTING THE DEVELOPMENT AND ACCESS OF ENABLING TECHNOLOGIES**

**MARC STANLEY**

Acting Director of the Advanced Technology (ATP), National Institute of Standards and Technology (NIST), United States

The Advanced Technology Program (ATP) funds high-risk, enabling technologies with the potential for broad-based benefits to accrue to the United States. Since its inception in 1990, ATP has played a major role in developing platform technologies in such areas as drug discovery methods, tissue engineering, DNA diagnostics, and xenotransplantation all of which may provide solutions to pressing medical problems. In accelerating the development of innovative technologies through partnerships with the private sector, the ATP (administered by the National Institute of Standards and Technology and a part of the U.S. Department of Commerce) fulfills public interests and objectives. In his talk, Acting Director Marc Stanley will address the role ATP has played in the development of emerging technologies as well as its role in promoting the broad access and uptake of such technologies.

## **WHY PRIVATE/PUBLIC PARTNERSHIPS FOR R&D? INDUSTRY PERSPECTIVES**

**DAVID E. WEBBER**

International Federation of Pharmaceutical Manufacturers, Switzerland

The paper presented will commence by covering some of the realities confronting R&D Directors in the pharmaceutical industry. The processes by which R&D priorities are set within companies will be discussed in this context.

Next, the real needs for additional R&D in those diseases most prevalent in developing countries will be discussed. It is important that the challenges that do exist are viewed in proportion to the scale of the problem.

The concept of 'corporate social responsibility' (CSR) provides a helpful overall framing of companies activities in areas that are 'non-commercial'. The specific area of Public-Private Partnerships (PPPs) for product R&D will be reviewed

PPPs such as the Medicines for Malaria Venture (MMV) are advancing well, and industry's support for this approach explained. The essential components of such PPPs will be discussed, along with the challenges that these initiatives face. Alternative schemas will be discussed.

**PARTNERSHIPS BETWEEN PHARMACEUTICAL COMPANIES AND INTERNATIONAL  
AND GOVERNMENTAL AGENCIES FOR RESEARCH AND DEVELOPMENT ON  
NEGLECTED DISEASES**

**ROY WIDDUS**

Project Manager, Initiative on Public-Private Partnerships for Health/Global Forum  
for Health Research, Switzerland

Innovative collaborations targeting diseases of the poor have existed for over two decades, dramatically increasing in number recently. They typically include public/governmental; private not-for-profit; and private for-profit organizations. They are defined – and distinguished from commercial ‘partnerships’ – by the fact that they address products for diseases where market forces, and typically health services delivery systems are not functional. Hence they include ‘access’ to their intended products as part of their mission, beyond R & D.

Such public-private partnerships are extremely varied in participants, legal status, mode of operations, and size. They are funded at present mostly by bilateral aid agencies and philanthropies, but at a level that is sub-optimal. They, however, “add-value” because they recruit the essential product development expertise existing only in industry at costs lower than the market rates for such facilities, expertise and other resources (*e.g.*, access to compound libraries).

Expectations on such ‘partnerships’ are probably unreasonably high considering their level of funding at present.