The global need for effective antibiotics—A summary of plenary presentations

Gunnar Alvan a,∗, Charlotta Edlund b, Andreas Heddini a

a ReAct, Action on Antibiotic Resistance, Uppsala University, SE-751 05 Uppsala, Sweden
b Medical Products Agency, SE-75103 Uppsala, Sweden

A B S T R A C T

To highlight the global need for effective antibiotics and explore possible concerted actions for change, cross-cutting plenary sessions served to frame the program of the conference. These sessions contained presentations on the present state of antibacterial resistance and the availability, the use and misuse of antibiotics. A number of possible actions were discussed, such as rational use of and access to antibiotics from various perspectives. The roles of vaccines and diagnostics were touched upon and followed by in-depth discussions on supply-side bottlenecks with their scientific, regulatory and financial challenges. The value chain for research and development (R&D) of antibiotics has to be reengineered if we are to realize the development of much needed new antibiotics. This challenge will require a multitude of actions, some of which are related to changing the financial realities of antibiotics and interventions by global and regional institutions.

1. Background
1.1. Setting the scene: the global picture of antibiotic resistance

The antibiotic era in clinical medicine was launched more than 70 years ago with the introduction of sulfonamides. However, the major breakthrough was the mass production of penicillin during the Second World War. Professor Otto Cars, chairman of Action on Antibiotic Resistance (ReAct), Sweden, underlined that the stunning success of penicillin which meant a drastic increase in survival from bacterial infections, clearly changed the world (Fletcher, 1984). However, there were already early warning signs of what was to come. As early as 1942, René Dubos predicted that bacterial resistance should be expected. “Rather than counter bacterial resistance with even more potent weapons”, he argued that we should, “seek instead more peaceful coexistence with pathogens” (Moberg, 1996). When Alexander Fleming (Fleming, 1945) received the Nobel Prize in 1945, he noted, “it is not difficult to make microbes resistant to penicillin”.

Resistance develops by spontaneous mutations or through horizontal transfer of resistance genes. In large bacterial populations (e.g., the gut flora) small subpopulations of resistant bacteria will be selected and amplified by antibiotic treatment that kills susceptible bacteria. The selection process has been ongoing since the beginning of the antibiotic era and has contributed to an increasing gene pool of resistance in the commensal flora, in hospitals, in the community and in the general environment. Through indiscriminate use, ignorance and complacency, this valuable resource has been squandered and the consequences are now becoming increasingly apparent. Presently, at least 25,000 patients in Europe die per year because their bacterial infections are not treatable with available antibiotics (ECDC/EMEA, 2009). It is a fact that many advanced treatments that we today take for granted (e.g., cancer chemotherapy, care for preterm babies, transplantation and major surgery) cannot take place without the support of effective antibiotics.

The situation in developing and low-income areas is worrisome. Poverty, overcrowding, extremely poor housing, malnutrition, contaminated food and the lack of clean water create a basis for transmission of pathogens. In addition, healthcare systems are weak or non-existing in these environments, and antibiotics are often sold and used without medical consultation. As always, poor people suffer most in all respects, as so amply pointed out by Professor Zulfiqar Bhutta, Aga Khan University, Pakistan. Infections in infants, such as diarrhea and pneumonia, are the cause of 40% of the death toll in this age group in underprivileged areas. Diarrhea that is caused by Shigella, salmonellosis and cholerics takes the lead and the resistance to antibiotics (such as ciprofloxacin) increases rapidly in those pathogens. Resistance data is not complete for the

© 2011 Elsevier Ltd. All rights reserved.
whole world, but the available information is cause for alarm and action. The increase of antimicrobial resistance worldwide is then an imperative challenge for those who want to improve health and quality of life for the inhabitants in all parts of the world. This will negatively influence the possibilities to attain the health-related Millennium Development Goals (MDGs).

1.2. Reflections from a global perspective

Dr. Guenaël Rodier, WHO Regional Office for Europe, emphasized that although there is a serious deficiency of global data on antimicrobial resistance, available information shows an alarming increase in resistance affecting all infectious agents. To take multidrug resistant tuberculosis (TB) as an example, globally 440,000 cases are estimated to have occurred in 2008 while a mere 7% of these were actually notified in the official WHO statistics. The malpractice of antibiotics can be characterized as overuse, underuse and wrong-use! Antimicrobial resistance spreads through healthcare associated infections, usually associated with weak healthcare systems. Dr. Rodier further noted the absence of global momentum, both in the action to improve rational use of antibiotics and infection control and in the development of new antibiotics. However, the main strategic components should be surveillance, prevention, containment, research and innovation. A coordinated global response is sorely needed in which “nobody is exempt from the problem or from playing a part in the solution”.

2. Policy challenges to optimizing the use of antibiotics

2.1. Reaching for global access and affordability

The currently biggest problem in low-income countries is the lack of knowledge and presence of misconceptions among the people. Dr. Eva Ombaka, senior consultant and former director of the Ecumenical Pharmaceutical Network, observed that there is some overlooked resources that can be used much more. For example, cell phones are widely available in these environments and there is some limited access to and use of the Internet, especially by the youth. These means can be much more and innovatively used, including using cell phones to pass correct/urgent information to isolated areas. A possible downside is that sick people may source and use unreliable health information from the Internet. A second aspect is the purchase and use of drugs from a “drug shop”, where drugs, including antibiotics, are generally freely available. However, the service providers are often not professionally trained and the drugs are of questionable quality-substandard or counterfeit! It remains that the public at large needs to be informed about use of drugs and mobilized to demand and practice better health behavior. For example, prescription drugs should be administered only on prescription, and the right of any medical doctor or other health worker to prescribe any existing drug should be questioned. Alliances will be necessary to bring about change.

2.2. Rational use: where less is more

Professor Roger Finch, University of Nottingham, UK stated that, for many types of major global infection, there is clearly a therapeutic failure because available treatments are not effective enough. Among these infections are TB, MRSA infections, hepatitis B and C, HIV and most diseases that exist in tropical areas. Better and faster diagnostics would be of great help in selecting most appropriate treatment and in reducing empirical prescribing. To improve disease management electronic support could be employed to improve the quality of prescribing and facilitating linkage of data from diagnostic tests, drug use and outcomes. The drugs presently available should be treated with great caution to preserve their value and thus extend their useful life. Regulatory Authorities have a key role to play in ensuring that generic/off-label drugs have indications appropriate to current clinical needs. Concerted and sustained international collaboration is necessary to effect these changes.

2.3. Perspectives on rational use and access

Dr. Ramanan Laxminarayan, Director of the Global Antibiotic Resistance Partnership, USA, presented an economist’s perspective on the actual challenges and found bacterial disease persisting as a major killer. The consumption of antibiotics increases globally in that there is, in addition to much restricted availability because of poverty, an increasing middle class of people who have economic means to buy what they think they need. Dr. Niyada Kiatying-Angsulee, Chulangkorn University, Thailand emphasized perspectives on regional “network of network” from South East Asia involving the establishment of a national alliance, an institute surveillance system and the promotion of rational antibiotic use. Dr. Dana Hanson, World Medical Association, USA, discussed the commitment of physicians as expressed by the World Medical Association to progress based on professional skill and solidarity.

3. Global priority-setting for research and development to manage antibiotic resistance

3.1. Introduction

The session was opened by Professor Zulfiqar Bhutta who stressed the need for an action-based agenda that would take innovation to where it is needed most. The roles of vaccines, diagnostics and antibiotics in relation to bacterial resistance were discussed by Dr. John Clemens, International Vaccine Institute, South Korea, Professor Rosanna Peeling, London School of Hygiene and Tropical Medicine, UK and Dr. Andreas Heddini, ReAct, Sweden. They addressed the state of the current pipeline, identified gaps and included a forward-looking discussion about prioritization of these technologies and their respective and combined potential values.

It has become increasingly clear that antibiotic resistance is a multi-dimensional, complex problem, the roots of which span over many scientific areas and sectors of society. There will not be one magic bullet solution to resolve antibiotic resistance, but rather a variety of counter measures and actions targeting different aspects of the problem. Although antibiotics are by far not the ultimate solution to the problem of bacterial infections, they will be a mainstay in their management. Thus, the question is not whether we need new antibiotics – because we do – but by which mechanisms they should be developed to ensure that any new health technology or product is addressing a global need and that aspects of access and affordability are considered in the process. In addressing antibiotic resistance the targeting several areas is essential:

- Improved rational use (which in principle equals more restrictive use in both human and non-human sectors).
- Improved infection control/hospital hygiene.
- Development of novel antibiotics and complementary technologies (i.e., vaccines and new and/or improved diagnostic methods).

3.2. Pneumococcal vaccines

Strategies to manage antibiotic resistance require combined efforts using several available resources in the health system. Prevention of disease can be achieved through a number of measures, where vaccination stands out as a highly cost-effective intervention. *Streptococcus pneumoniae* is one significant pathogen in which
ongoing efforts to develop more effective vaccines could prove useful in mitigating resistance. *S. pneumoniae* is the most common cause of community-acquired bacterial pneumonia, meningitis and bacteremia in children and adults, with approximately 1.6 million deaths worldwide per annum. Multidrug resistance (≥3 antibiotic classes) is reported worldwide, constituting a majority of *S. pneumoniae* isolates in many countries.

New-generation conjugate vaccines have demonstrated the ability to prevent antibiotic-resistant pneumococcal colonization and disease via direct and herd effects. Employment of these vaccines has also been shown to reduce overall use of antibiotics, which together may synergize to lower the circulation of antibiotic-resistant pneumococci. However, the introduction of pneumococcal conjugate vaccines has induced an increase in circulating “replacement” serotypes, including those resistant to antibiotics. One of these replacement serotypes, 19a, has been documented to have acquired increased levels of antibiotic resistance and to have caused increased rates of invasive pneumococcal disease. Future strategies to contain antibiotic-resistant pneumococcal infections will therefore have to include increasingly broad vaccine serotype-coverage in conjunction with aggressive policies to ensure appropriate use of antimicrobial drugs.

### 3.3. Development of diagnostics for drug-resistant infections

Increasing access to appropriate treatments for infectious diseases would have a major impact on disease burden, particularly in low-income settings. Because of the lack of rapid diagnostic tests, most common infections have to be managed empirically in accordance with the clinical picture. This causes and drives unnecessary and erroneous antibiotic use, which could have been avoided by the availability of appropriate diagnostic tests. The landscape of diagnostic tests is characterized by a lack of investment in diagnostics research and development (R&D) with little industry interest in diagnostics R&D on diseases prevalent in low-income countries. This low level of interest is due to a perceived lack of return for investment, i.e., pharmaceutical companies are commercial and therefore tend to develop medicines with profit in mind. There is also lack of access to diagnostic services, lack of regulatory transparency and control, as well as inadequate quality standards for test evaluations. Diagnostics are often undervalued. Recent data from the US show that while diagnostics comprise less than 5% of hospital costs and about 1.6% of all Medicare costs, their findings influence as much as 60–70% of decision making in health care.

During recent years, however, several novel diagnostics based on molecular techniques have been developed. These techniques include automated extraction and real-time polymerase chain reaction (PCR) amplification techniques, as well as innovative “lab-on-a-chip” platforms in which thousands of patient samples can be screened for resistance profiles within a matter of hours. Thus, many high quality diagnostics for infectious diseases are available but they are neither affordable nor accessible to most patients in the developing world where disease burden is the greatest. There is an urgent need to increase diagnostic capacity at all levels of the healthcare system to provide accurate, evidence-based management for such major syndromes as fever and lower respiratory tract infections.

Another area requiring better diagnostics is surveillance of antibiotic resistance. Today, surveillance activities are disproportionately geared toward high-income countries and hospital settings. There is a need to establish surveillance networks to cover hot spots where antibiotic resistance will likely emerge, including resource-poor settings. This is also important for the development of new diagnostic tools in which novel biomarkers for early detection of treatment failure could be identified. There is great need for highly sensitive and specific tests in a high throughput format, low technical complexity and for use with non-invasive specimens. Some options for diagnostics at different levels of care include:

- For screening at hospitals
  - Point-of-care (POC) tests for admission
  - Highly sensitive and specific assays for local outbreak investigations and epidemiology studies
- For patient management
  - POC tests to distinguish between viral/bacterial/fungal infections
  - Detection of pathogens within a syndrome and their antimicrobial susceptibility pattern
- For surveillance of resistance
  - Standardized and systematic collections of specimens
  - Highly sensitive and specific tests in high throughput format, low technical complexity

In addition, there is an unmet need for innovative mechanisms to accelerate product development, clinical trials and regulatory approval of new diagnostics as demonstrated in a survey from 2002 carried out by WHO/TDR. The survey showed that more than 50% of countries worldwide lack regulatory oversight for diagnostics but for the WHO/AFRO region, the figure was a staggering 73%.

### 3.4. The need for antibiotics with novel mechanisms of action

Despite the magnitude of the resistance problem, little progress has been made in R&D for new antibacterial agents effective against resistant strains. For instance, only two new antibiotics had been developed in the past 10 years. Recent data suggests that the biological fitness cost associated with bacterial resistance to antibiotics may quickly be compensated for, i.e., resistance will continue even in the absence of antibiotic selective pressure. This further underscores the need for novel antibiotics.

The past 40 years have seen the emergence of only two new classes of antibiotics: oxazolidinones and cyclic lipopeptides, neither of which is effective against Gram-negative bacteria. The future for antibiotic drug development also appears bleak: among the top 15 pharmaceutical companies, which accounted for 93% of antibiotics placed on the market between 1980 and 2003, only 5 drugs in their R&D pipelines are antibacterials (ECDC/EMEA Technical Report, 2009).

It should be noted, however, that any public investment in drug development should be done in a framework of careful analysis looking at the different options to prioritize among health technologies and research goals to ensure greatest public benefit. Furthermore, should new classes of antibiotics be discovered, measures must be taken to prolong their shelf-life through rational use and a variety of measures related to drug selection, combination and dosage regimens. An exploration of such possibilities is found in this issue (Mouton et al., 2011).

The development of new antibiotics will require a sustained, systematic effort of discovery and development that spans over many years. Further, innovative financing mechanisms for clinical trials, which are very costly to undertake, should be explored. Finally, a mechanism for prioritizing among different antibiotics, diagnostics and other health technologies has been called for. Such a prioritizing framework needs to be based on global surveillance of antibiotic resistance to provide information on prevalence of resistant pathogens. This framework will also allow predictions over time, modeling and analysis of trends. Notably, such a framework cannot be rigid but should provide needs-based information to
underpin scientific agendas and guide public investments in R&D. Elements of such a framework could build in components, such as disease prevalence, mortality & morbidity, deaths averted by a new product, access to antibiotics and their use and risk/likelihood of success.

4. Supply-side bottlenecks: scientific, regulatory and financial challenges

4.1. Challenges in bringing innovation to market

The main reasons for the insufficient availability of novel and effective antibiotics are mainly considered in the scientific, regulatory and financial domains. Professor Anthony So, Duke University, USA reviewed the challenges of bringing innovations to the market. The decline in R&D is caused by a multitude of interplaying factors. The supply-side bottlenecks critically influence the value chain along the life cycle of antibiotics. Among the most difficult scientific and financial challenges is the success rate in the market, often referred to as “the valley of death”, i.e., the transition from preclinical to clinical phases. During the market life cycle of a drug, the return of investments (ROIs) must at least be anticipated to exceed the costs for R&D. Currently, the net present value (NPV) for an intravenous (i.v.) antibiotic is considered an order of magnitude less profitable than, e.g., drugs for musculoskeletal diseases. This is due to several factors, among which besides the acknowledged scientific challenges to develop novel antibiotic classes, other factors include the short treatment regimens and the curbs placed by prudent and rational use of effective antibiotics, the therapeutic competition posed by a relatively saturated market and the relatively higher profit margins on other therapeutic drug categories. Different scenarios apply to large pharmaceutical companies compared with small- and medium-sized firms (SMEs). SMEs may face different opportunity costs than research-based, multinational companies. If a start-up firm has a promising antibiotic but little else in its portfolio, it will not have alternative R&D opportunities that a large pharmaceutical firm is likely to have with a diverse R&D portfolio. In looking at the drug R&D landscape for neglected diseases a study of 63 projects found that half of these were being conducted by multinational companies, invariably on a “no profit, no loss” basis, and the rest by small-scale businesses in industrialized countries or developing country firms, with expectations of commercial return (Moran et al., 2005).

4.2. Scientific challenges

The scientific challenges and attrition rates of antibacterial discovery were elucidated by Dr. David Payne, Vice President, GSK, USA. The high expectations following the genomic breakthrough revealing numerous potential bacterial drug targets were followed by disillusionment and a poor success rate. The success rate of obtaining new chemical leads from these screens was only 7%, which is substantially lower than other therapeutic areas. There are several reasons for the difficulties, including the fact that most antibacterial targets are enzymes that are hard to inhibit: compound libraries are biased toward attributes suited for mammalian targets and the safety and spectrum challenges of antibacterial development, especially when it comes to Gram-negative bacteria. More innovative approaches are needed. Some areas currently being investigated include returning to natural product screening, exploring novel chemical space (e.g., boron chemistry) and development of antibiotic potentiators (e.g., efflux-pump inhibitors). Reviewing attrition rates of novel-mechanism antibacterial R&D, it is clear that improving the success rate of Phase 2 starts would improve delivery, but, in turn, this means longer timelines and the requirement of more resources to generate higher quality candidates. In addition, diagnostics could play a very impactful role at enriching clinical trials with the most appropriate patients to prove the attributes of a novel mechanism antibiotic (i.e., enrich for patients with clearly defined bacterial infections and patients with infections that are caused by multiresistant pathogens). Such a plan of action could enable smaller, cheaper clinical trials and improve regulatory outcomes.

Structure-based drug design for discovery of novel antibacterial drugs to circumvent some of the bottlenecks in the search for these antibiotics was suggested by Professor Ian Chopra, University of Leeds, UK. This innovative approach for the identification of new inhibitors of both classical and novel bacterial target proteins was predicted to increase the success rate for discovery of antibacterial drugs in the near future. Indeed, it may be possible to design molecules that simultaneously inhibit two or more functional sites in a target enzyme, which could minimize the potential for the development of resistance. It was stressed that the vast majority of current antibacterial drugs are of natural origin. A return to natural product screening was also desirable as an addition to exploring soil and marine biomass using metagenomic tools. Non-terrestrial opportunities might be considered in the future.

4.3. Regulatory perspectives

The regulatory agencies are often pointed out as having an essential role in the dwindling pipeline of new antibacterial agents. By setting up extensive regulatory barriers for the development program and data needed for approval of new drugs and new indications, the substantial investments needed and risks for a negative outcome will have a significant hampering effect on R&D in this field. Dr. Tomas Salmonson, vice-chair of the Committee for Human Medicinal Products-European Medicines Agency (CHMP-EMA), gave a presentation of the role of the regulatory agencies with special focus on the European situation. In this presentation, Dr. Salmonson shared his views of current and future possible regulatory measures needed to aid the development of antibiotics for which there is a high medical need. Following the GAP analysis (ECDC/EMA, 2009), jointly published by the EMA and ECDC (European Centre for Disease Prevention and Control) in 2009 in collaboration with ReAct highlighting the urgent need for novel antibacterial agents especially against multi-drug resistant Gram-negative pathogens, and the outcome of the European Union (EU) conference on this subject held in Stockholm September 2009 (Swedish Government, 2009), specific EU Council conclusions were adopted in December 2009 aiming for actions at both the national and European level, including regulatory efforts (Council of the European Union, 2009). Regulatory measures currently taken within the existing legal framework include the ongoing revision of EU regulatory guidelines for antibiotics, where further flexibility to facilitate drug development, such as the possibility of alternative study designs, was discussed. Sponsors are strongly advised to discuss with EU regulators as early as possible in the development program to optimize the path and chances for approval. It was stressed that a decision of approval is always based on a benefit–risk assessment, taking the specific situation for each product and indication into account. Possible regulatory measures inspired by the success of the Orphan drug regulation were discussed. A special designation of antibiotics for which a particular medical need exists coupled with attributed regulatory benefits may be a fruitful way forward. This approach has to be supported by specific EU legislation. It was emphasized that regulators are driven by the goal to enhance the development, availability and adequate use of effective and safe antibacterial agents.
4.4. Financial bottlenecks

The financial hurdles influencing the development of new antibiotics were further clarified by the fact that Big Pharma is currently ruled by the chase for blockbuster. However, it is almost an impossible task to assess the probability of technical success and market potential of a new drug, not to mention prizing 10–15 years ahead, since sales forecasts are wrong 80% of the time. The advice from Dr. Bernard Munos, former advisor in corporate strategy, Eli Lilly, USA, is to accept that forecasting is hopeless and to reposition R&D away from blockbuster and instead focus on breakthrough innovations. Medicines are for people, not for profits; however, profits always follow a true breakthrough drug. Funding should be restricted to breakthrough ideas and clinical development should only be initiated for genuine breakthroughs. The competence for breakthrough innovations and the competence for operational excellence are at crosscurrents in the sense that fixation on one degrades the capacity of the other.

4.5. The role of the pharmaceutical industry in meeting the public health threat of antibiotic resistance

The pharmaceutical industry is of course a major player in the search for new antibiotics and in meeting the public health threat of antimicrobial resistance. Novel ideas on how to combine the realities of commercial entities to the need of the public were proposed, suggesting a completely innovative concept to separate the financial return from the use of a product. This concept, published separately in this issue (Bergström, 2011), was presented by Dr. Richard Bergström, European Federation of Pharmaceutical Industries and Associations.

5. Reengineering the value chain for research and development of antibiotics

5.1. Introduction

This session, introduced by Professor Anthony So (Duke University, USA), focused on lessons drawn from the landscape of neglected diseases that might cross-apply to the R&D of antibiotics. All three initiatives involve public sector funding, two in product development partnerships. Created to help overcome market failures, product development partnerships mobilize both public and private sector resources to develop diagnostics, drugs and vaccines for neglected diseases. Most are disease-specific and even technology-specific in focus. Within the antibacterial space, the challenges of TB drug development may prove particularly instructive though there are both similarities and differences from antibiotic R&D more generally. However, as these examples illustrate, there is more to filling these R&D gaps than innovative public financing. The Global Alliance for Tuberculosis Drug Development is piloting a new regulatory pathway for testing combination therapies against TB. By testing combinations in parallel rather than serially, years might be shaved off the R&D pipeline. The Drugs for Neglected Diseases Initiative (DNDi) covers more than one disease, but primarily focuses on kinetoplastid diseases. DNDi’s experiences in aligning target product profiles with patient needs, building capacity for clinical trial platforms in disease-endemic countries and securing access to proprietary compound libraries may inform efforts for antibacterial drug discovery. Finally, taking a page from information technology, India’s Council on Scientific and Industrial Research (CSIR) has sought to apply the approach of open source innovation to TB drug discovery. Supported by public sector monies and tapping a network of Indian universities, this fledgling project has exciting promise.

5.2. The Global Alliance for TB Drug Development

Tuberculosis, although curable, continues to kill someone somewhere in the world about every 15 s – more than 5000 people every day, or two million this year alone. Because of increasing drug resistance, co-infection with HIV and long treatment periods with existing therapeutic regimens, there is a growing demand for new TB drugs. The principal agenda of The Global Alliance for TB Drug Development (TB Alliance) was explained by its president, Dr. Melvin Spigelman. The Alliance collaborates with research institutions and pharmaceutical companies to share risks, which provides an incentive for partners to collaborate. While retaining management oversight of its drug development projects, the TB Alliance outsources the development of potential drugs to public and private partners, providing funding and scientific guidance. Depending on the project, the TB Alliance either co-invests and co-develops a project, funds and manages it directly, or licenses the technology or intellectual property involved. Project diversity is a stated goal in which potential compounds are selected from a variety of chemical classes, with a wide range of targets within the TB organism, Mycobacterium tuberculosis. Currently, drug sensitive TB requires a regimen of 4 drugs administered for a period of six to nine months. Moreover, there are few available treatments for multidrug resistant TB and tolerability is a problem. Because many patients with TB suffer from HIV/AIDS, there are additional difficulties with anti-retroviral therapy (ART) and anti-TB drug co-administration. There are thus several unmet needs for shorter, simpler therapy, more effective and safer regimens and drugs that can be given together with ART. The TB Alliance has over 20 projects in its portfolio at different stages of discovery and development, ranging from lead identification to phase III clinical trials. A new paradigm is being developed for rational selection and development of new combinations with the aim of significantly shortening the time of new regimen development.

5.3. Applying lessons from neglected diseases

DNDi is a non-profit drug R&D organization that is developing new treatments for neglected diseases. Dr. Jean-Pierre Paccaud, DNDi, Switzerland, explained the “needs-driven” approach that facilitates basic science, preclinical and clinical research on targeted diseases. The organization’s current target diseases include malaria and the three most neglected diseases caused by the protozoan group known as the kinetoplastids: visceral leishmaniasis (VL), sleeping sickness (human African trypanosomiasis, HAT) and Chagas disease. DNDi’s primary objective is to deliver 6–8 new treatments by 2014 for VL, HAT, Chagas disease and malaria, as well as to establish a strong R&D portfolio addressing patient treatment needs. To date, DNDi registered two fixed-dose combination treatments for malaria, a new combination regimen to treat sleeping sickness and a VL combination treatment deployed in Africa. The organization strives to use and strengthen existing capacity in disease-endemic countries via project implementation. A further aim of the model is to mobilize the private sector through incentives/rewards and partnerships built on a strong collaborative basis:

- At early discovery stage:

- Compounds come mainly from Pharma partners
- Biological characterizations are conducted at major parasitology research centers ("reference centers")
- Pre-clinical development with dedicated CROs, etc.

- Clinical trials:
  - Collaborating partners include institutions and experts from disease-endemic countries, health authorities, regulatory experts, and frequently, MSF teams

- Registration and manufacturing:
  - Pharmaceutical partners provide essential capabilities to ensure sustainability
  - Technology transfer for production in Southern countries

The concept of patient-centered Target Product Profiles (TPPs) is central to ensure needs-driven R&D. The TPP details the characteristics of the product to be developed, provides guidance throughout the drug development program and establishes stringent go-no-go criteria to insure that the drug developed fully responds to the patient's needs in terms of efficacy, usability in the field and affordability. DNDI's patient-centered TPPs, which are shared between all partners, have been critical for focused and efficient drug development.

Also of great impact on drug accessibility, careful management of intellectual property (IP) and licenses rights is paramount to insuring access.

5.4. India's open source drug discovery initiative

India's open source drug discovery initiative (OSDD) was communicated by Professor Samir Brahmacari, director general, Council of scientific and industrial research, India. OSDD is a novel model for drug discovery based on concepts from open source in information technology (IT) and proposes a new, non-proprietary way of taking leads through the early phases of discovery. Examples include the OSDD where a web-enabled open source platform – both computational and experimental – has been established to make drug discovery cost effective and affordable by using the collective creative potential of students and scientists worldwide. Participants are rewarded with incentives for developing novel algorithms, finding drug targets, leading identification and other contributions. A current project is focused on discovering drugs for TB and making them available to patients at an affordable cost. Although the genome of this pathogen was sequenced 10 years ago, the function of more than 1000 of its 4000 genes remains unknown, opening challenging possibilities in the search for new treatments. To eliminate this problem OSDD recently launched the "Connect-to-Decode" open-source initiative. Within weeks, 830 qualified scientists volunteered to reannotate the entire *M. tuberculosis* genome. The OSDD consortium brings together more than 4300 individuals from 130 countries at the virtual project platform and through sequence based comparison between human genome, human oral and gut flora, more than 50 potential drug targets have been identified excluding leads with potential effects on commensal bacteria. OSDD has been able to create a small molecule open access repository. The virtual platform operates at the modest cost of approximately USD 2 million per annum.

6. Future treatment options – balancing antibiotics with other treatment concepts

Basic research into completely novel antibacterials that do not belong to the established groups of antibiotics has sparked global interest over recent years (Fernbro, 2011). However, interesting as they may be, few, if any, of these compounds have delivered as promised. Antibacterial peptides are the effector molecules of innate immunity and over the past few decades, the search for new drugs and drug targets has prompted an interest in these compounds. Small molecules, on the other hand, can interfere with bacterial virulence factors and secretion pathways that can relieve severe or pathogenic symptoms without killing bacteria. In addition, the normal flora would be left unharmed. Bacteriophages have been used and tested extensively throughout the 20th century, most notably in the countries of Eastern Europe, but many studies have later been deemed to be of unsatisfactory quality and hence the probability of a breakthrough in the near future seems unrealistic.

The prospects of alternative strategies to combat bacterial diseases were further reviewed by Professor Staffan Normark, Karolinska Institutet, Sweden. Professor Normark offered an update of the current scientific platform for alternative strategies (e.g., virulence factor inhibitors, boosting the clearing efficacy in the host, antimicrobial proteins and immunotherapy with human monoclonal antibodies). The approach of using small molecules to inhibit virulence factors of pneumococci and *Staphylococcus aureus* and blocking of type III secretion in Gram-negatives are currently "hot" areas of research. Antimicrobial peptides and phage therapy are still investigated; however, several hurdles in terms of stability and specificity remain in these areas. Existing drugs (such as statins and morphine) can affect the clearing capacity in the host, which should be further investigated. Stimulating the endogenous expression of antimicrobial peptides and the phagocyte function has been shown to be feasible in animal models. However, future prospects were not deemed very optimistic for any of these alternative strategies. At most, these strategies will generally provide add-on therapy to current drugs in a subset of patients, particularly in those with a compromised immune system.

Thus, although new lines of research are looking promising and may produce novel treatment options in the future, these are far from being adequately developed. In a foreseeable future, antibiotics will be the mainstay for treatment of severe bacterial infections, which further emphasizes the pressing need for new classes of antibiotics.

7. Moving toward concerted action

Dr. Bernardus Ganter, adviser, antimicrobial resistance, WHO regional office for Europe, explained the features of antimicrobial resistance that make it "a faceless" disease in that it appears as an abstract threat to treatment and prophylaxis with properties that make it hard to define and grasp. A solution to this communication problem could be to call it "difficult to treat bacteria". It is for certain that there is now an arrival of new strains that are virtually resistant to all existing antibiotic drugs. This is a frightening prospect in light of the decreasing development of new antibiotics. In developing countries there is stagnation in reaching the United Nation's Millennium Development Goals on childhood survival while in emerging economies an increased affordability of antibiotics of varying quality can be seen as well as highly questionable medical rationality.

Steps have been taken by the WHO to approach the problem of increasing bacterial resistance (e.g., the WHO Global Strategy for Containment of Antimicrobial Resistance from 2001). In 2009, a WHO resolution was adopted on the Prevention and Control of Multidrug Resistant TB. This strategy contains the necessary principle of making drugs against TB available only on prescription. We all look forward to the World Health Day in 2011 which will be dedicated to antimicrobial resistance. In Europe, an Antibiotic Awareness Day has been proclaimed for the 18th of November each.
year. USA and Canada will follow Europe’s initiative with their own awareness days. On this day, a number of meetings will be held that will include discussions about antimicrobial resistance, how it develops, what actions to take, how to broaden the knowledge and how to initiate a call for action among health care professionals.

Mario Nagtaam, policy officer, EU Commission, Belgium, reflected on a number of policy initiatives, recommendations and conclusions within the EU following the Council Conclusions taken by the European Health Council on December 1, 2009. As a response, the European Commission is working on an EU action plan, including, among other issues, possible incentives for the development of novel effective antibiotics. This development was preceded by an expert conference organized by the Swedish Government during its presidency in the EU in the autumn of 2009. In the aftermath of the conference the issue of antimicrobial resistance was discussed at the EU–US summit. The Swedish Prime Minister, Mr. Reinfeldt, and President Obama agreed to form a taskforce, the Transatlantic Task Force on Antimicrobial Resistance (TATFAR). The TATFAR will deliver its final report in March 2011.

The Swedish EU presidency meeting focused on new incentives for the development of novel antibiotics. An extensive review, “Policies and incentives for promoting innovation in antibiotic research”, was commissioned from the European Observatory on Health Systems and Policies and the London School of Economics. The essentials of the report were later published (Morel and Mossialos, 2010). The present meeting, “Global need for effective antibiotics – Moving towards concerted action”, can be viewed as a follow-up to the Swedish EU presidency meeting.

In the EU there is mandatory, harmonized monitoring of antimicrobial resistance (European Antimicrobial Resistance Surveillance Network, EARS-Net) coordinated by the European Centre for Disease Prevention and Control (ECDC) in Stockholm, Sweden, as described by Dominique Monnet, senior expert and coordinator of ECDC’s program on antimicrobial resistance and healthcare-associated infections. Similar activities are taking place in the US where the Centers for Disease Control and Prevention (CDC), Atlanta, GA, collaborate with different states to collect data on prevalence of resistance in health care and other settings. This and other data from patients in Europe, the US and elsewhere show the recent emergence and spread of bacteria that are totally or almost totally resistant to all available antibiotics!

Dr. Anna Lönnroth, acting head of unit, EU Commission, Belgium, expanded on the work of the TATFAR. The objectives of the TATFAR are to (1) increase mutual understanding of US and EU activities and programs on antimicrobial issues, (2) deepen the transatlantic dialogue, (3) provide opportunities to learn from each other and (4) promote information exchange, coordination and cooperation between the US and EU member states. The TATFAR has several working groups dealing with the appropriate therapeutic use of antibacterial drugs, prevention of drug resistant infections and strategies to improve the pipeline of new antibacterial drugs. Its final report is expected in March 2011.

Dr. Dennis Dixon, Chief of the Bacteriology and Mycology Branch at the National Institute of Allergy and Infectious Diseases, USA, asserted that the US National Institutes of Health have a robust research agenda in antimicrobial resistance addressing basic, translational and clinical research. In addition to the standard, investigator-initiated research opportunities there are specific antimicrobial resistance-focused opportunities, including product development partnerships that require academic scientists to collaborate with small and large companies to move promising diagnostics, vaccine and therapeutics through preclinical development. One example of a clinical research initiative, “Targeted Clinical Trials to Reduce the Risk of Antimicrobial Resistance”, aims to generate data to guide optimal use of existing antimicrobials, thereby prolonging their lifespan. Ongoing trials funded under this initiative focus on dose, duration, pharmacokinetic and pharmacodynamic (PK/PD) and the absolute need for antimicrobials in disease areas subject to the greatest antimicrobial use. Additionally, a range of preclinical and clinical services, which are free and available to the international research community, have been established to fill gaps along the product development pipeline.

In conclusion, antibiotic resistance is a complex and truly global problem that requires global solutions through concerted action.

References


