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RESEARCH AND DEVELOPMENT FOR NEGLECTED DISEASES

In India, diseases burden have been divided into three major categories – communicable diseases, maternal and child health conditions (together these contribute approximately half the burden) and second to these are the non-communicable diseases[1]. India therefore is shouldering the diseases of both – the developed world (diabetes melllitus and cardiovascular diseases) as well as that of the developing world (infectious and neglected diseases). The resurgence of well-controlled diseases like malaria, leishmaniasis and other vector-borne conditions affect the poor and rural population significantly. However, these diseases have been neglected world wide as they primarily affect the weaker section of the population[2]. Hence it will be pertinent to say that neglected diseases are a group of parasitic and other infectious diseases, that have usually been on low priority for the pharmaceutical sector and primarily affects the poorest of the poor section of community[3].

The neglected diseases such as leishmaniasis, chagas disease, human African trypanosomiasis, malaria, tuberculosis and autoimmune deficiency syndrome wreak havoc on the populations of the developing world. But significantly less attention has been paid on research and development of new drugs for these neglected diseases. Though the global spending on health research has increased dramatically from $30 billion in 1986 to $106 billion today, yet 90% of this allocation is being spent on the health problems of less than 10% of the world's population. In fact only 10% of the world's health research expenditure is incurred on 90% of the global health burden – the now well-established concept of the 10/90 gap[4]. This gap has led to the lack of drug development and innovative treatments for the diseases afflicting the poor.

The high cost of discovering new therapies has discouraged global pharmaceutical companies from investing into these non-lucrative areas. As a result, these neglected diseases are a persistent cause of serious health issues to populations in the developing countries.

The economic burden of infectious diseases per person measured in disability-adjusted life years(DALYs) is twice as compared to that in the established market economies or the developed countries. Besides, over 40% of the healthy years lost in the developing countries are attributable to communicable, maternal, and perinatal diseases, many of which never existed or have been all but eradicated in the established market economies.

Research into new drugs for these diseases remains inadequate and many of the current treatments have adverse drug reactions, are expensive, and becoming increasingly ineffective, even though the communicable diseases in resource-limited settings continue to cause disaster.

Of the total number of new drugs developed during 1975 to 2004 only 1.3% (20 new drugs)were for tropical disease and tuberculosis, which accounts for approximately 12% of diseases burden (Box 1). These figures emphasize the lack of interest in drug development for neglected diseases and a growing gulf between the development of drugs for tropical and non-tropical diseases, resulting in a fatal imbalance in the research trends. This trend in the drug development is a result of the profit oriented and patent-driven drug development system, which does not cater to people suffering from neglected diseases, as they are not considered a profitable market. However, it is not just the market that is responsible for this sorry state of affairs, but public policy makers have also neglected research and development of new drugs for these diseases[5]. The health needs and disease patterns of different socioeconomic groups and geographical locations are different and therefore require different attention and programmes.

NEGLECTED DISEASES: FACTS AT A GLANCE.

- 60 million people are at risk of contracting sleeping sickness, but treatment options are few.
- Kala-azar kills 60,000 people each year, but the most common treatment was developed in the 1930s.
- Nearly 1,400 children die every day of AIDS-related complications, but existing methods to diagnose HIV in infants are ill-adapted for poor countries, and only a few paediatric formulations of antiretrovirals exist.
- TB is responsible for nearly 2 million deaths each year but treatment depends on increasingly ineffective drugs dating back the 1950-1960s. The most common test developed in 1882 detects the disease only in 45-60% of cases.
- 340 million sexually transmitted infections occur every year but many cannot be treated due to lack of simple and reliable tests.

The Indian Council of Medical Research (ICMR) has been concerned to this situation and therefore joined hands in the efforts to address the problem of lack of drugs for neglected diseases and mobilise resources for R&D directed towards finding new treatments for people affected by these diseases. Drugs for Neglected Diseases initiatives (DNDi) was established in 2003 by seven partners – four major public research institutions from developing countries viz. (i) the Indian Council for Medical Research, New Delhi (ii) the Oswaldo Cruz Foundation from Brazil, (iii) the Kenya Medical Research Institute; and (iv) the Ministry of Health of Malaysia. The remaining three partners are private research organisations - the Pasteur Institute, WHO's Special–Programme for Research and Training in Tropical Diseases-TDR (permanent observer on the DNDi Board); and Médecins Sans Frontières (MSF)–the humanitarian medical aid charity that first voiced the need for an organisation such as DNDi. The Drugs for Neglected Diseases initiative (DNDi), a Swiss Foundation, is implementing a different model of research and development that closely involves the countries touched by these diseases[6].

Each of the seven founding partners contributes to DNDi's operations with financial or in-kind contributions. DNDi aims to take the development of drugs for neglected diseases out of the marketplace and encourage the public sector to assume greater responsibility. Its main objective is to develop and make available drugs for neglected diseases on a not-for-profit basis. The DNDi has been established to develop projects in response to the needs of neglected patients. The DNDi aims to obtain between six to eight new drugs and treatments before 2014, for which it needs to invest nearly 255 million US dollars. To achieve this it is trying to build a needs-driven portfolio of short, medium and long-term R&D projects, raising awareness about the issues and strengthening R&D capacity by carrying out projects in countries where the diseases are endemic.

The DNDi also works with the pharmaceutical industry and academics to speed up and manage the research and development processes for drugs for neglected diseases and believes that the pharmaceutical and biotech sectors have a role to play in this process. The aim is to work with developing countries for strengthening their research and development capacities. This can be further enhanced by collaboration with developed countries and finding solutions within the regions and

not just subsidising developed country industry. Although industry and academics develop medicines and private foundations often provide resources, the global direction and prioritisation of public health needs and priorities must be led by the public sector. For promoting the development of drugs an open approach compared to the patent has been established as higher levels of intellectual property protection have not resulted in increased drug R&D for global health needs. With the collaboration with the world's largest medical humanitarian organisation - the MSF, as founding partner, DNDi has direct access to the real needs of patients in the field as well as to the distribution mechanisms for medicines because the DNDi's main objective is to develop drugs keeping in view the needs of the patients.

Collaborative Model

The DNDi's main strengths are that it is a virtual organisation working closely with countries affected by endemic tropical diseases. It has at its disposal a growing network of academic and industry expertise from both developing and developed countries. These experts are pooling their know-how in parasitology and clinical trials, experience of treating neglected disease patients, and drug manufacturing capacity, to ultimately move drugs stuck in the pipeline in the early stages of development, through clinical trials to the patients. The process of drug development is cost-intensive and requires a dedicated team and continued effort. It has been observed that chemical compounds with proven potential in animals studies have not been carried forward.

The DNDi parent group is based in Geneva. It also has regional networks in Asia, Africa, Japan, India and Latin America that actively advocate for the initiative, provide information on local expertise and capacity, and support DNDi projects in the regions. In its quest for new therapeutic options for neglected diseases, DNDi also hopes to make use of the human and scientific resources of pharmaceutical and biotech companies (large or small) wherever high-quality research and development facilities are accessible. Pharmaceutical companies are indispensable to DNDi's success, as they possess vast repositories of molecules, the means to move from development to industrial production, and with highly specialised teams of researchers.

The discovery of new potential drug candidates in experimental studies requires sustained research by a dedicated team, which is expensive, with the associated risk of project attrition along the way to develop it into a drug. The selection from hit to lead candidate requires synthesis and evaluation of various compounds. The candidate selected is further evaluated for its pharmacological and toxicological potential. It's mutagenic, carcinogenic and genotoxic effects are determined prior to human administration for its safety profile. The next stage is clinical trial after the animal data is reviewed and evaluated by regulators for use in humans.

The DNDi is spreading its drug development programme by investing resources in a balanced portfolio of projects at different stages of the drug development process: from early discovery research on new targets and compounds and implementing a series of studies to prepare adequate registration dossiers on therapeutic compounds used for different indications. This mixed portfolio of long, medium and short-term projects will allow the initiative to have a quicker and more tangible impact.

The DNDi identifies promising projects in two ways– by organising calls for letters to the scientific community for funding of collaborative projects and via a continuous survey of published literature and proactive contact with researchers in the field of infectious diseases. This process enables the scientists with potential interest and capacities to get involved in the development of drug. With a proactive approach the partnerships are established with scientific and industrial institutions to work in collaboration to develop new molecules

Portfolio

The DNDi's current projects were identified by responses to calls for letters of intent for proposals from scientist interested in research in neglected diseases. These were evaluated by an independent Scientific Advisory Committee. The calls also serve to draw the attention of the scientific community to the need for more research on neglected diseases and to identify potential collaborative partners. DNDi's project portfolio currently holds twenty projects at different stages of development to address identified needs for the treatment of various diseases like visceral leishmaniasis, sleeping sickness, Chagas disease, and malaria. The projects are subjected to continuous assessment and follow up by DNDi, and must meet the milestones. The work is to be completed during the given tenure set by

the Scientific Advisory Committee in order to receive continued DNDi assistance.

Each project is supported for an initial period (mutually decided between DNDi and the principal investigators of the projects) and will continue to be managed by DNDi and evaluated periodically. The project with potential will be taken to the drug development stage.

The DNDi's efforts to develop a project portfolio are managed by a small Research and Development team. By using existing research facilities in both developed and developing countries and by collaborating with scientists in public and private research institutions, DNDi facilitates the R&D process and strengthens R&D capacity and capability in disease-endemic regions via the implementation of its projects. This model of multi-level collaboration will help accelerate the R&D process so that afflicted patients in poorer countries can have faster recourse to better, more effective drugs.

In India collaboration has been established with various research institutions for discovery phase projects where scientists are involved in synthesis and evaluation of potential compounds for neglected diseases. This collaboration has been established with the Central Drug Research Institute, Lucknow and the Indian Institute of Chemical Biology, Kolkata. The prevalence of malaria and leishmaniasis in our country has been a cause of concern as these affect the regions, which are backward and underdeveloped. The DNDi in collaboration with ICMR is planning to initiate clinical trials to implement newer treatment regimens in the form of combination drug therapy especially for malaria as has been recommended by the World Health Organization[7]. Efforts made by DNDi to address the problem of lack of effective drugs for treating malaria and leishmaniasis, prevalent in India are highlighted in this write-up.

TUBERCULOSIS

- Every year, 2 million people die of TB and 8 million people develop active TB.
- One third of the world is currently infected, and 16 million suffer daily from active TB.
- 95% of TB cases and 98% of TB deaths occur in poor countries. The epidemic is expected to worsen in the next few years, especially in Africa and southeast Asia.
- Every year over 1.5 million people acquire active TB in sub-Saharan Africa. This number is rising rapidly as a result of the HIV/AIDS epidemic: TB is an opportunistic disease that preys on HIV-positive people whose immune systems are weakened.
- TB is a leading cause of death among people with AIDS, and in some regions of Africa, three-quarters of TB patients are HIV-infected.
- TB spreads through the air and is highly contagious. On an average, a person with infectious TB infects 10-15 others every year.
- People infected with TB do not necessarily become ill - the immune system creates a barrier around the bacilli which can remain dormant for years. 10% of infected people (who do not have HIV/AIDS) develop active TB at some point during their lifetime.
- The currently recommended treatment is a drug combination that must be taken for 6-8 months.
- Nearly 40% of the Indian population of all ages has *Mycobacterium tuberculosis* infection, approximately 85 lakh people have TB at any given time and 400000 die each year with tuberculosis.

MALARIA

The disease bruden of malaria is difficult to assess, because of the common symptom of fever and dynamic nature of the disease. The present national surveillance systems usually assess the trend of malaria rather than exact burden of the disease.

The number of malaria deaths in the world has been estimated to be between 1.1-1.3 million. Based on reported data and the estimates of populations at risk and the incidence rates, it is estimated that the malaria incidence in 2004 was between 350 - 500 million cases. Malaria is considered to be endemic in 107 countries and territories[8].

The tropical Africa–south of the Sahara accounts for approximately 90 percent of the world's malaria deaths. The Plasmodium falciparum malaria is the most dangerous predominantly transmitted by vectors that are highly efficient. The rest of the 10% cases are reported from countries outside Africa. Of there, nearly 3 million cases are reported from India and Pakistan.

Traditionally, entire India is endemic for malaria except areas 1,500 m above medial sea level (msl) and some coastal areas. In 1953, 75 million cases

MALARIA

- Malaria kills between 1 and 2 million people every year. The most vulnerable are young children in remote rural areas, pregnant women, and refugees.
- Malaria kills one African child every 30 seconds
- Malaria is the first cause of death for children under 5 years of age
- Sickness and death from malaria account for 30-50% of hospital admissions and a yearly loss of US $412 billion on the African continent
- In many African countries resistance to chloroquine and sulphadoxine-pyrimethamine (SP) is so high that both drugs are virtually useless. For example, in 1999, Tanzania had chloroquine resistance rates from 28-97%, Kenya 66-87% and Uganda 10-80%.
- In India the falciparum and drug resistant malaria is rising and there is underreporting of the cases as it is not mandatory to file data by private sector.

with 0.8 million deaths were reported from India. With launching of the National Malaria Control Programme and the introduction of DDT, the cases dropped to 0.1 million in the 1960s and the entire country was brought under the National Malaria Eradication Programme (NMEP). However, there was a resurgence and 6.47 million cases were reported in 1976. Consequent to this, major changes were introduced by initiating a modified plan of operation. The concept of voluntary managed drug distribution centers and fever treatment depots was introduced[9]. This led to improvement in the malaria situation, and malaria cases stabilized at around 2-3 million cases from 1983 onwards. However, the decline was in vivax malaria and the proportion of P. falciparum has gradually increased to about 45% by 1996. The increase in Pf percentage could be due to number of causes viz., environmental changes, inadequate treatment, and inadequate/ineffective intervention measures for transmission control. The proportion of Pf cases to total malaria positive cases during the period 1996-2001 has been around 47% but this does not include the cases treated by the private and not for profit health services.

At present, in India malaria endemic regions are unevenly distributed across the country. India's 80% population now lives in areas with low incidence of malaria. The rest of the 20% population has 80% malaria cases[8]. Orissa has the highest number of malaria cases and deaths in the country. The burden of disease is higher in Gujarat, West Bengal, Chhattisgarh, Madhya Pradesh, Rajasthan, Uttar Pradesh, Karnataka, Jharkhand and and and Maharashtra also[10]. In the year 2003, India reported 1.86 million confirmed cases and 1000 deaths. Of these, 45% or about 850,000, were cases of falciparum malaria[11-17]. Falciparum malaria is emerging in India extensively with rising trend in the resistance to the presently administered drug chloroquine[11].

World Health Organization Southeast Asian Regional Office estimates six times more cases of malaria. The wide disparity in the figures for positive malaria cases reported by the National Vector Borne Disease Control Programme may be partly because the bulk of malaria cases are treated by the private practitioners as fever cases and not reported to health departments.

Drug resistance may be defined as the persistence of parasites after treatment by an antimalarial. Drug resistance in India is mostly against chloroquine as this has been used extensively. The north-east states have been showing a high level of drug resistance.

The WHO has recommended combining of conventional antimalarial drugs with artemisinin derivatives like oral artesunate for the treatment of P. falciparum malaria[7]. The rationale is that combining drugs with independent modes of action improves their efficacy. The combination also helps in retarding the development of resistance because of the mutual drug protection as the modes of action of both the drugs are different. The concept that the development of drug resistance could be prevented by the combination of drugs with independent modes of action was developed first with respect to the treatment of tuberculosis, and later adopted for leprosy, cancer and AIDS therapy. The possibility that antimalarial drug resistance could be prevented by the use of combinations of unrelated antimalarial drugs was pioneered by Peters[18].

Data from WHO/TDR trials showed that adding oral artesunate to a standard antimalarial was beneficial in terms of improved efficacy and reducing gametocyte carriage[16]. Efficacy in absolute terms was, however, related to the efficacy of the partner drug. However,

Table. Results of amodiaquine alone or combined with oral artesunate (4mg/kg/d x3d) for the treatment of falciparum malaria in African chldren.

	Kenya		Senegal		Gabon	
	AQ/AS N=200*	AQ N=200	AQ/AS N=160	AQ N=161	AQ/AS N=110	AQ N=110
Cure rates Day 14	175/192 (91%)	140/188 (75%)	148/160 (93%)	147/157 (94%)	92/94 (98%)	86/96 (90%)
Cure rates Day 28 (PCR uncorrected)	123/180 (68%)	75/183 (41%)	130/159 (82%)	123/156 (79%)	80/94 (85%)	70/98 (71%)
PCR corrected**	144/180 (80%)	98/183 (54%)			85/94 (89%)	77/98 (77%)

*N = number recruited
** Missing PCR data = failures
Significant P values : 1<0.0001, 2 =0.016, 3<0.0001, 6=0.02

the usefulness of artesunate (AS) based combinations remains to be established in sub-Saharan Africa, where malaria transmission is much more intense than in southeast Asia. The data for the three studies of AS combined with amodiaquine(AQ) are presented in table.

Based on the promising results, artesunate (AS) combined with amodiaquine(AQ) seems to be a good candidate to develop further as a fixed dose. In the meantime, several African countries e.g. Burundi, Cameroon, Equitorial Guinea, Gabon, Ghana, Liberia, Mali, Sao Tome, Sierra Leone, South Sudan, Zanzibar, and one Asian country, Indonesia are beginning to deploy the co blister of artesunate and amodiaquine as national policy.

The reasons for increased acceptances of fixed dose combinations, in general and the ASAQ and ASMQ fixed tablets, in particular, to patients are as follows:

- Fewer tablets to take
- Drug regimen easier to understand
- Drug regimen easier to take or administer for mothers to children
- Both components are taken together, once a day
- Reduction in the daily dose of MQ may reduce the incidence of dose related side effects
- There is no need to time the doses with food

LEISHMANIASIS

- Leishmaniasis is endemic in 88 countries with an estimated 350 million people at risk.
- Around 2 million people become ill with leishmaniasis every year. Only 30% of this number is officially reported.
- An estimated 12 million people are currently affected by leishmaniasis in its different forms.
- The most severe form, visceral leishmaniasis or kala-azar, is a fatal disease. Without treatment, all of the estimated 500,000 people affected annually will die.
- In 1999, 57,000 deaths were reported due to VL, but the real number is thought to be significantly higher.
- Ninety per cent kala-azar cases occur in five developing countries: India, Bangladesh, Brazil, Nepal and Sudan.
- Kala-azar also occurs in Europe. In Southern Europe, over 1,600 people have been diagnosed as infected with both kala-azar and HIV up to early 1999. Intravenous drug users represented 71% of this number.

In India DNDi and ICMR are initiating a clinical trial to evaluate the combination drugs therapy as recommended by the World Health Oraganisation. Two new fixed-dose artemisinin-based combination therapies (FACTs) - artesunate-amodiaquine (AS/AQ) and artesunate-mefloquine (AS/MQ) have been developed by DNDi and will be available by the end of this year. These tablets offer greater choice to patients and will cost approximately 50% less compared to current ACTs.

The DNDi's innovative FACT project has brought together academic, public and private partners from around the world. Europe's leading drug maker, Sanofi-Aventis, will develop AS/AQ for sub-Saharan Africa and Indonesia.Farmanguinhos, the public pharmaceutical branch of the Oswaldo Cruz Foundation, Brazil will produce AS/MQ for Latin America. The ICMR has taken lead to facilitate conducting clinical trial with DNDi for evaluating the drug efficacy of these combinations in India for malaria .

Leishmaniasis

Kala azar or visceral leishmaniasis (VL) has re-emerged from near eradication. The annual estimate for the incidence and prevalence of kala-azar cases worldwide is 0.5 million and 2.5 million, respectively.It is endemic in 62 countries. Of these, 90% of the confirmed cases occur in India, Nepal, Bangladesh and Sudan[19]. In India, it is a serious problem in Bihar, West Bengal and eastern Uttar Pradesh. There is under-reporting of cases as the official figures are likely to grossly underestimate the actual cases as a large number of patients are treated by the private health professionals. Untreated cases of kala-azar are associated with up to 90% mortality, which with treatment reduces to 15%. Even in specialized hospitals mortality is approximately 3.4%. It is also associated with up to 20% subclinical infection. Lymphadenopathy (enlargement of the lymph glands), a major presenting feature in India raises the possibility of a new vector or a variant of the disease. The widespread co-existence of malaria and kala-azar in Bihar may lead to a difficulty in diagnosis and inappropriate treatment. In addition, reports of the organism developing resistance to sodium antimony gluconate--the main drug for treatment of kala azar would make its eradication difficult. Spraying of DDT helped in control of kala-azar; however, there are reports of the vector Phlebotomus argentipes developing resistance[20-22]. A combination of sandfly control, detection and treatment of patients and prevention of drug resistance is the best approach for controlling kala-azar[23].

AIDS

- AIDS is caused by the human immunodeficiency virus (HIV).
- Worldwide, 60 million people have been infected since the AIDS epidemic began.
- Of the estimated 40 million people currently infected with HIV, 28 million live in sub-Saharan Africa.
- AIDS carries a pervasive stigma in many societies. HIV positive people are often rejected by their families, fired from their jobs, and even denied care at hospitals.
- AIDS cripples the economic development of entire countries, because it often strikes people during their most productive working years.
- The disease has orphaned thirteen million children.
- The high numbers of AIDS patients further strains already overburdened health care systems.
- AIDS can be treated with antiretroviral drugs that stop the virus from replicating, but do not kill it. This treatment is still not widely available in developing countries.

The diagnosis and treatment follow up of patients is a challenge for the doctors as presently the treatment period is twenty-eight days. The diagnosis is routinely done by spleen aspirate, which is difficult and invasive procedure requiring a basic clinic infrastructure. The drugs available for VL with established efficacy are all parenteral and an oral drug miltefosine has recently been approved in India. The most extensively used and till now the mainstay of therapy are antimonial drugs that are highly toxic and cannot be used due to development of resistance. Amphotericin B and pentamidine are second line drugs, which are more toxic and difficult to administer. The newer liposomal formulation of amphotericin B is less toxic and effective but is very expensive. Paromomycin is another injectable drug, which is undergoing clinical trial and has shown promising efficacy but needs further post marketing evaluation.

To reduce cost, duration and development of resistance, the combination of the anti-leishmaniasis drug is the immediate need of patient and goal of DNDi. For visceral leishmaniasis the DNDi has Indian partners

for generating the efficacy and safety data with respect to the most appropriate combinations that are approved by the regulators and scientifically validated. The ICMR and DNDi will collaborate in conducting the clinical trials for evaluating these combinations.

India' role in the Future: the Road Ahead

India has shown its innovative capacity in developing manufacturing processes for drugs, which require a substantial knowledge of chemistry and its application. This capability has been aptly applied to provide medicines at a lower price to the developing world. This is an area where available knowledge can be utilized to provide cost effective drugs for the neglected diseases. The vision for drug discovery in India looks clear as it can be sourced with traditional strengths in informatics and chemistry combined with emerging strengths in structural biology and post-genomic technologies. A few Indian institutions and companies have already had global impact on drug innovation; reveal the success factors and future promise for this sector in India. This can be further enhanced by working together with the best minds at global level.

India's strength is large number of skilled scientists and excellent facilities with the country's large and diverse population. The advantage India has is the capacity and developing capabilities in the field of conducting clinical trials. The cost of conducting clinical trials from phase I through IV is approximately 50 to 60% less in India.

The Government of India is supporting further clinical trials by updating the Schedule 'Y', Drugs and Cosmetics Act and facilitating global multi-center clinical trials throughout the country. Provisions have been made and guidelines prepared for recombinant DNA and other products, which could be a major incentive for global partners to conduct clinical trials for biologics in India.

India has to expand its ability and expertise, from generic and speciality contract manufacturing to innovative drug discovery and development in its own right. ICMR, through its collaboration with DNDi is shaping the vision for drug development and innovations. This will initiate collaboration with international laboratories and pharmaceutical industries to innovate drugs for neglected diseases thereby helping decrease the disparity in disease control between various economic strata of population.

References

1. NCMH Background Papers. Burden of Disease in India. National Commission on Macroeconomics and Health ... www.who.int/entity/macrohealth/action/NCMH_Burden.

2. Pecoul, B., Chirac, P., Trouiller P,, and Pinel, J. Access to essential drugs in poor countries: a lost battle? J Am Med Assoc 281(4)S: 361, 1999.

3. Guerin, PJ., Nosten F., and White, N. J. An essential R&D agenda. in the crisis of neglected diseases: developing treatment and ensuring access. Médecins Sans Frontières/DND Working Group, New York, March: 1-23, 2002 Available from: http://www.neglecteddiseases.org/1-1.pdf

4. Trouiller, P.,Olliaro, P,, Torreele E. Orbinski J., Laing R. and Ford N. Drug development for neglected diseases: a deficient market and public-health policy failure. Lancet 359, 22: 2002.

5. Dentico ,N. and Ford, N. The courage to change the rules: a proposal for an essential health R&D treaty. Plos Med 2: 14, 2005.

6. Drugs for Negelected Diseases Initiative. www.dndi.org (Accessed November 2005).

7. WHO. Antimalarial drug combination therapy.WHO/CDS/RBM/2001.35

8. WHO Health Report, 2004. www.who.int./whr/2004/en (Accessed November 2005).

9. Sharma, V.P. Return of parasitic diseases. J Parasit Dis 19 : 1, 1995.

10. Situation of malaria in India. www.namp.gov.in/malaria

11. Satpathy, S.K., Jena, R.C., Sharma, R.S., and Sharma, R.C. Status of Plasmodium falciparum resistance to chloroquine in Orissa. J Com Dis 29: 145, 1997.

12. Nongkynrih, B., Patro, B.K., and Pandav, C.S.Current status of communicable and non-communicable diseases in India. J Assoc Phys India 52:118, 2004.

13. Mohapatra, P.K., Namchoom, N.S., Prakash, A, Bhattacharya, D.R., Goswami, B.K., and Mahanta J.Therapeutic efficacy of anti-malarials in Plasmodium falciparum malaria in an Indo-Myanmar border area of Arunachal Pradesh. Indian J Med Res 118:71, 2003.

14. Tyagi, B.K. A review of the emergence of Plasmodium falciparum-dominated malaria in irrigated areas of the Thar Desert, India. Acta Tropica 89: 227, 2004.

15. Dev,V., Bhattacharyya, P.C., and Talukdar, R.Transmission of malaria and its control in the northeastern region of India.J Assoc Phys India 51: 1073 2003.

16. Adjuik, M., Babiker, A., Garner, P., Olliaro P., Taylor, W. and White, N.International Artemisinin Study Group. Artesunate combinations for treatment of malaria: meta-analysis. Lancet 363: 9, 2004.

17. WHO. The use of antimalarial drugs. Report of an informal consultation. WHO/CDS/RBM/2001.33

18. Peters ,W. The prevention of antimalarial drug resistance. Pharmacol Ther 47: 499, 1990.

19. Guerin, P.J., Olliaro, P., Sundar, S., boelart, M., Croft, S. L, Desjeux, P., Wasunna, M.K. and Bryceson, D. M. Visceral leihmaniasis: current status of control, diagnosis, and treatment, and a proposed research and development agenda. Lancet Infect Dis 2: 494, 2002.

20. Thakur, C.P. Socio-economics of visceral leishmaniasis in Bihar (India). Trans R Soc Trop Med Hyg 94: 156, 2000.

21. Sundar, S,. More, D.K., Singh, M.K., et al. Failure of pentavalent antimony in visceral leishmaniasis in India: report from the center of the Indian epidemic. Clin Infect Dis 31: 1104, 2000.

22. Sundar, S. Drug resistance in Indian visceral leishmaniasis. Trop Med Int Health 2001 6: 849, 2001.

23. Bryceson, A. Current issues in the treatment of visceral leishmaniasis. Med Microbiol Immunol 190: 81 , 2001.

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ABSTRACTS

Some Research Projects Completed Recently

Comparative cost analysis of health expenditure between tobacco smoker and non-smoker families in an urban slum

A family based study was carried out in ward 23 of Howrah Municipal Corporation area inhabiting community of heterogenous culture of low socio-economic groups sharing the some life style. The smokers families (1729) were treated as experimental group whereas non-smokers (1463) and control group, selected on the basis of vandom sampling. The aim of the study was to determine the costs in relation to health expenditure am0ong tobacco smokers and non-smokers as well as find out the cost component of family expenditure in relation to health for smokers and non-smokers.

The study revealed that the number of cigarettes smoked did not significantly change in the experimental group except in two cases, there was a reduction in after severe attacks of bronchitis. Nevertheless burden of the diseases due to smoking was found to be increased with consequent increase of economic loss because of cumulative effect of smoking for 3 years.It was noticed that in families who reduced the smoking, the morbidity of smoker as well as the family members also reduced signifying smoking is contributable to ill health implicating considerable expenditure.

On the other hand, among the smokers in the experimental group who continued smoking, the number of episodes of their illness as well as their family members increased significantly (P0.05) than the previous years consequently enhancing their expenditure. These findings are of enormous importance since with continued smoking, the smokers do suffer from repeated chronic obstructive pulmonary disease (COPD) leading to severe emphysema resulting in permanent disability causing loss of work and loss of earnings in addition to morbidity cost.

The study did show that on average cost of illness in experimental group was more not only when compared to control group but also in subsequent phases.

Thus the study reveals clearly that continuous smoking for years do damage the health of the individuals implicating higher and higher cost of illness compared to non-smokers.

The morbidity pattern due to smoking was almost same, except proportional increase in the morbidity due

to acute respiratory infection, COPD, hypertension peptic ulcer, coronary head disease compared to the previous phases. This was due to continuous effect of exposure from smoking.

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Reversal of multidrug resistance in cancer by the application of new resistance modifying agent

The study was carried out to develop and identify nontoxic resistance modifying agents (RMAs) from the study of structure activity relationship and develop effective chemotherapy by overcoming multidrug resistance.

Some novel resistance modifying agents based on organic molecules, Schiffs bases and metal complexes of Schiffs bases were developed. These organic compounds and metal chelates with organic ligands were synthesized and their structures elucidated through detailed spectroscopic studies like uv,ir, proton NMR, C13NMR, LC-MS, EPR. The novel RMAs were tested against a number of drug resistant cancer cell lines like EAC/Dox, S 180/Dox, 3-LL, CEM/ADR1000 (P-Glycoprotein-Expressing T Cell Acute Lymphoblastic CEM Leukemia Cells), HL60/AR (mrp-expressing). All these RMAs were capable of overcoming MDR in vitro and in vivo. The most important RMA, CuNG increases lifespan of the drug resistant cancer bearing Swiss mice to nearly 323% (T/C). the Mechanism of resistance reversal properties of the RMAs has been worked out and compared against the approved RMAs. Another potential RMA, Cobalt N-(2-hydroxy acetophenone) glycinate (CoNG) overcomes MDR in vivo. Copper N-(2-hydroxy acetophenone) glycinate (CuNG) showed maximal potential as RMA in vivo. CuNG, and some other RMAs showed glutathione (GSH) depleting properties and the RMAs affected the cellular expression of GST, MRP1, MRO2, gst-pi, gst-mu in EAC/Dox as well as other cells and thus achieved reversal of MDR. CuNG and some organic compounds like oxalyl bis (N-phenyl) hydroxamic acid (OBPHA) tested against P-gp expressing CEM-ADR cells. OBPHA were found to be effective in P-gp mediated MDR. Metal chelates having the potential as RMA were reported for the first time. The entire signaling mechanism involving drug resistance and its reversal by CuNG/CoNG, etc. requires further study. This may provide new leads in ongoing fight against MDR in cancer as novel target proteins may be discovered.

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ICMR NEWS

The following meetings of various technical groups/ committees were held:

Task Forces (TFs)/Expert Groups (EGs)/and other Meetings

TF on Genetic Basis of Resistance to Diabetes in Raica Community	January 6, 2006
TF on Jai Vigyan Mission Mode on RF/RHD	January 11, 2006
EG on Urban Mental Health Problems and their Service Needs	January 13, 2006
TF on Human Genetics Projects	January 23, 2006
Core Committee on Neurology	February 7, 2006
EG on Task Force Project on Mental Health Service Needs and Service Delivery Models in Disaster (Earthquake) affected Population in Gujarat	February 10, 2006

Project Review Committees (PRCs):

PRC on Otorhinolaryngology	January 16, 2006

PRC on Orthopaedics, Adverse Drug Reaction, Biomedical Engineering	February 1, 2006
PRC on Oral Health	February 20, 2006
PRC on Pharmacology	February 23, 2006
Special PRC on North-East Projects	February 25, 2006

Participation of ICMR Scientists in Scientific Events

Dr. R.B. Colah, Deputy Director and Dr. Anita Nadkarni Research Officer, Institute of Immunohaematology, Mumbai, participated in the X International Conference of Thalassaemia and Haemoglobinopathies and XII International TIF Conference for patients and parents at Dubai (January 7-10, 2006).

Dr.D.S. Dinesh, Research Officer, Rajendra Memorial Research Institute of Medical Sciences, Patna, participated in the I KALANET meeting at Antwerpen (January 24-30, 2006).

Dr.K.V.R. Sarma, Deputy Director and Dr. G.M. Subba Rao, Research Officer, National Institute of Nutrition, Hyderabad, participated in the Review and Evaluation meeting on the Regional Training Course on Inter-Sectoral Food and Nutrition Plans and Policies, at Johannesburg (January 30-31, 2006).

Dr. R. Rama Krishnan, Assistant Director, National Institute of Epidemiology, Chennai, participated in the Conference on Technical Consultation on HIV Vaccine Clinical Trial Design, at New York (January 31 - February 2, 2006).

Shri P.S. Shah, Research Officer, National Institute of Virology, Pune, participated in a meeting to Plan and Discuss experiments with Dr. Monita at the Institute of Tropical Medicine, Nagasaki University (February 5-10, 2006).

Dr. Smita S. Kulkarni, Senior Research Officer, National AIDS Research Institute (NARI), Pune, participated in the Good Clinical Laboratory Practices Workshop at Johannesburg (February 6-8, 2006).

Dr. Dipika Sur, Deputy Director, National Institute of Cholera and Enteric Diseases (NICED), Kolkata, participated in the VIII Commonwealth Congress on Diarrhoea and Malnutrition, at Dhaka (February 6-8, 2006).

Dr. Hema Joshi, Assistant Director, National Institute of Malaria Research, Delhi, participated in the meeting of Tafenoquine P. vivax Advisory Board at Bangkok (February 13-14, 2006).

Dr. R.J. Yadav, Deputy Director, National Institute of Medical Statistics, New Delhi, participated in the training of WHO in Epidemiology and Biostatistics at Khon Kaen University, Thailand (January 16 - February 24, 2006)

Dr. S.M. Mehendale, Deputy Director (Senior Grade), Dr. A.R. Risbud, Deputy Director, Dr. Seema Sahay, Senior Research Officers Dr. Smita Joshi, and Dr. Sheela Godbole, Research officers, NARI, Pune, participated in the Annual HPTN meeting at Washington, D.C. (February 18-24, 2006).

Dr. S.K. Niyogi, and Dr. T. Ramamurthy, Deputy Directors, NICED, Kolkata, participated in a discussion with Prof. S. Yamasaki, Professor of Prevention of International Epidemics at Osaka Prefecture University, Osaka, Japan on characterization of Antimicrobial Resistance among Enteric Pathogens (February 20-25, 2006).

Workshop

A WHO Workshop on Prevention and Control of Non-communicable Diseases and Diet was held at Baroda. (January 24-25, 2006).

Appointments

Dr. S.K. Bhattacharya, Director of Council's National Institute of Cholera and Enteric Diseases, Kolkata and a World Famous Scientist on Diarrhoeal Diseases took over as Additional Director-General of ICMR w.e.f. February 22, 2006.

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I, J.N. Mathur, hereby declare that the particulars given above are true to the best of my knowledge and belief.

Sd/- J.N. Mathur
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Childhood Hodgkin's disease: Role of Epstein-barr virus association, cellular proliferation and apoptosis parameters in relation with the treatment outcome

A retrospective study was undertaken to elucide proliferation index, apoptosis-related gene products, apoptotic index and Epstein Barr virus (EBV) association in Indian children with Hodgkin's lymphoma (HL) and their respective correlations with clinical, pathological factors and treatment outcome. Paraffin embedded lymph node (LN) biopsies of previously untreated children diagnosed with HL from 1991 to 2003 were stained immunohistochemically with primary monoclonal antibodies against CD45, CD20, CD45RO, CD15 and CD30 antigens for WHO classification, Mi*B-1, bak, bcl-2 and p53. EBV was detected by immunohistochemistry (IHC) and in situ hybridization (ISH). Apoptotic index of tumour cells was studied technique. Patients were treated with chemotherapy alone and analysed for response and survival.