

## PROCEEDINGS OF FIFTH INTERNATIONAL SYMPOSIUM ON TYPHOID FEVER HELD AT THE AGA KHAN UNIVERSITY KARACHI-PAKISTAN

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The Fifth International Symposium on Typhoid Fever and other Salmonellosis was held at the Aga Khan University, Karachi, Pakistan from February 5-7th 2002. The meeting was organized in collaboration with the World Health Organization. It was preceded by workshops on molecular methods in the epidemiology and Diagnosis of Typhoid. The symposium attracted over thirty foreign delegates from eleven countries besides participants from all over Pakistan.

The symposium was formally inaugurated by Federal Minister for Science and Technology, Government of Pakistan, Prof. Atta ur Rehman in the evening of February 5th. Speaking at the occasion he said that Typhoid Fever is a poor man's disease. Pharmaceutical industry finds it difficult to invest in this area because they do not sell these drugs to recover their investment. It is a problem for many areas of tropical diseases. There is very little investment in research because of huge cost of Research and Development. It requires sophisticated know how which is only available with the big multinational pharma companies. Hepatitis is another area. Now there is resurgence of interest in natural material like medicinal plants. Prof. Atta ur Rehman suggested that a National Study Group should be constituted to work together in different fields in tropical diseases like Typhoid, Hepatitis, Leshmeniasis, and Epilepsy

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etc. These groups will need facilities and research support. This is the area where we can help them. We have a committee, which evaluates the research projects for grants. We have faculties of analytical tools at H. E. J. Institute of Chemistry at Karachi University but there is a need to constitute a focus group on different tropical diseases.

Dr. Robert Baker Provost of AKU in his speech said that often it is extremely difficult to organize such meetings at places where such diseases are more prevalent because of the negative images projected overseas which are highly exaggerated. We had an extremely successful workshop and hope the conference will also provide lot of useful information for the participants. According to WHO seventeen million new cases of typhoid fever are reported globally each year. Pakistan is among the high-risk countries including South Asia. Emergence of resistance strains is a serious problem. Typhoid fever has become a public health emergency for which multiple resources can be harnessed, he added.

Earlier Prof. Z. A. Bhutta, Prof. of Pediatrics at AKU and Chairman of the Organizing Committee in his welcome address said that this meeting began as a small and select gathering of scientists interested in Typhoid Fever in Kuala Lumpur led by Dr. Tikki Pang over a decade ago. It has now grown to represent the definitive global meeting on this subject. In the past meetings were held at Bangkok, Bali and Taiwan. The current meeting being the fifth, is distinguished by the fact that we have also

organized a pre-conference workshop on "Molecular methods in the epidemiology and diagnosis of typhoid fever" which was attended by thirty young microbiologists and molecular biologists.

Prof. Bhutta also narrated the enormous difficulties faced while organizing this symposium in view of the geopolitical situation in the region. He thanked all those who made it

**Typhoid Fever has emerged as a major public health problem in many developing countries**

possible to come despite all the negative images. He specially thanked Wellcome Trust UK, NIBGE in Faisalabad, International Vaccine Institute and the Centers for Disease Control USA for their help and assistance. To many people, typhoid, Prof. Bhutta said, represented a challenge which was largely met through public health measures such as clean water and sanitation. However they fail to take into account the enormous opportunities that technology and modern science provides us in understanding the epidemiology, spread and severity of this disease. He also referred to the slow progress in research on typhoid fever in comparison to other technologies. The most commonly used diagnostic test Widal test is now a century old while progress in vaccine research for typhoid has also lagged behind other disorders. We hope to harness science and technology for the control of typhoid fever using biotechnology research for diagnostics as well as for vaccine development.

#### GLOBAL STATUS OF TYPHOID FEVER

Dr. Bernard Ivanoff from International Vaccine Institute Seoul, South Korea was the keynote speaker in the inaugural session. Speaking about global status of typhoid fever, Dr. Ivanoff said that current recommendations for prevention of enteric diseases are effective when they are properly applied. Typhoid Fever, he said, is a major public health problem in the developing countries. The emergence of antibiotic re-

sistance has created a very serious situation. Now effective vaccines against typhoid fever are available and new improved vaccines are under development. The available vaccines should be used in nurseries and school age children besides public health measures to control these diseases, which accounts for major morbidity and mortality.

Typhoid, Dr. Bernard Ivanoff said is responsible for millions of deaths every year. This is an old disease transmitted by fecally contaminated water and food in endemic areas in particular by carriers handling food in developed countries. C.A. Louis reported its first clinical symptoms in 1829 while Ebert discovered the etiologic agent in 1880. Even hundred years later this enteric infection still remains a public health problem in developing countries. Typhoid fever disappeared from Europe and North America due to improvement of water treatment and sanitation installations by the end of first half of the 20th century. However in developing countries typhoid fever still accounts for an estimated 600,000 deaths per year. The peak incidence is reported in children from 3-19 years of age although in countries like India, Jordan, Bangladesh and Nigeria it has been reported much earlier.

Since 1990 there are more and more strains of *S. Typhi* that are resistant not only to most previously useful oral antibiotics like chloram-

**Public health measures, antibiotic therapy and prevention through vaccines are essential for its control**  
- Dr. Bernard Ivanoff

phenicol, ampicillin and cotrimoxazol but to new molecules like ciprofloxacin and ceftriazone. At the same time decrease in multidrug resistant strains has been reported from endemic countries like Bangladesh. The existing mix of interventions like health education and antibiotics treatment is unlikely to eliminate completely the problem of typhoid fever. For this complementary efforts to develop effective tools for public health control of the disease are essential, Dr. Ivanoff remarked.

Talking about the availability of vaccines against typhoid fever, Dr. Bernard Ivanoff said that the first vaccine was tested in England in 1896 more than hundred years ago. However, despite several successful attempts no existing vaccine is currently used in routine immunization to control typhoid fever in endemic areas. The available vaccine includes the Vi and the Ty21A. Vi can be mixed with Hepatitis -A, Yellow Fever and Rabies vaccines to reduce the cost. Ty21A requires three doses two days apart. Seven years after vaccination, it has over 67% protection efficacy. It can also be combined with OPV polio and yellow fever vaccines.

The future vaccines, he opined, should be one dose vaccine, effective in adults and children. One of the vaccines currently tested offers 91%

**Typhoid Fever is a major public health problem in Asia. Officials agree for introducing vaccines but are reluctant to introduce new generation of typhoid vaccines - Dr. Tikki Pang**

protection after twenty-seven months follow up. There is another vaccine, which requires two doses six weeks apart. Clinical microbiologists and travelers must get vaccination against typhoid fever. People living in refugee camps and children were another important group, which must be vaccinated against typhoid fever. Similarly vaccination is important in outbreak situations and in endemic areas. It is not true that vaccination does not work in outbreak situations and in endemic areas as studies have showed its protection and efficacy up to 71-72% in Thailand and Uzbekistan. It is also a wrong notion that typhoid vaccine is expensive. WHO Dr. Bernard Ivanoff said recommends that all school age children must get vaccine for typhoid fever, he added.

#### PLENARY SESSION-A

Dr. Anwar Nasim along with Dr. Franklin White chaired this session. Dr. Gordon Dougan from Imperial College London was the keynote speaker who talked about recent sci-

entific advances in typhoid fever and also highlighted the areas where progress will be made in the next three to five years. Speaking about pathogenesis of salmonella he pointed out that it is exclusively a human pathogen, hence S. Typhi is an exclusively a human disease. Control of typhoid will be dependent on improving public health systems in endemic areas. Improving public facilities is of critical importance along with the availability of better diagnostic tools, vaccines and antimicrobial agents. Recent genetic analysis has shown that S. Typhi isolates from around the world are highly related but not identical. Examination of genomes also provides information as to why the bacteria are restricted to infecting one host.

Typhoid as a disease, he stated, is relatively of recent origin. He then discussed some significant S. Typhi pseudogenes as well as future for bacterial classification of bacterial genotyping. Wellcome Centre in Vietnam, he said, is currently conducting studies on Human Genetics of Typhoid. Salmonella is able to survive and replicate. A human DNA micro assay with 24,000 genes monitoring the impact of infecting human THP-1 Cells with Vi positive and Vi negative salmonella Typhi. In future there are plans to use this to obtain a gene print of human typhoid. During the discussion it was stated that in future cancer patients will demand treatment and it will derive the fascinating technology to hospitals. Its cost will also come down dramatically.

#### PLENARY SESSION-B

This session was chaired by Dr. Gordon Dougan from UK along with Prof A.G. Billoo

**More work is needed to prove that Hepatitis-C increases the susceptibility of typhoid fever**

from AKU. Dr. Tikki Pang from WHO spoke about the DOMI program for Typhoid Fever. DOMI (Diseases of the Most Impoverished) programme is coordinated by the International Vaccine Institute (IVI) and is funded by the Bill and Mclinda Gates Foundation. It is designed

to accelerate the introduction of new generation vaccines against cholera, shigellosis and typhoid fever into developing countries of Asia. It is also intended to evaluate the newer gen-

**Blood culture should be asked even if the patient has taken some antibiotics in case of suspected cases of typhoid**  
- Dr. Mohsin Ahmad

eration of experimental vaccines. The components of DOMI programme include establishment and dissemination of disease burden data and vaccine cost effectiveness calculations, as well as behavioral vaccines use, assurance of adequate and competitive vaccine supply. In order to accomplish these goals the DOMI is being coordinated with WHO and Ministries of Health involving prominent scientists in each collaborating country, which includes Bangladesh, China, Indonesia, India, Pakistan, Thailand and Vietnam.

Vi vaccines, he pointed out are most effective for developing countries keeping in view their safety, efficacy and single dose. However, we have to convince the decision makers so that this vaccine is used more. Local production of Vi vaccines is also cost effective, he added. He then discussed the Vi effectiveness studies, technology assistance in Good Manufacturing Practices of Vaccines and social service research. Speaking about Vi effectiveness during outbreaks, he referred to the multicenter studies planned in China, Indonesia, Pakistan and other countries. Vi effectiveness optional research was also discussed. The DOMI Typhoid Program is targeting Vi vaccine for accelerated introduction into public health programme. This is a unique multidisciplinary, coordinated program to generate evidence that help policy makers in Asia to make rational decisions about use of modern typhoid vaccines. This project will cover a total population of approximately 250,000; disability burden assessment; cost effectiveness analyses, technical assistance in vaccine production and regulation, policy and economic studies of vaccine introduction besides behavioral studies of vaccine acceptability. He concluded his

presentation by stating that Typhoid Fever is a major public health problem in Asia. Officials agree for introducing vaccines but are reluctant to introduce new generation of typhoid vaccines.

During the discussion it was pointed out that use of oral vaccine is associated with some problems like giving three capsules on alternate days. The considerations are mostly operational. Patient may not come for the second or the third dose. As such single dose Vi is very effective and cheap as well. However both vaccines i.e. the oral one and the Vi are good. Vi vaccine is selected for mass vaccination but for children, oral vaccine may be preferred. Since the objective is to get quick results, that is why we selected Vi vaccine, Dr. Tikki added.

Dr. Sajjad Mirza from Pakistan discussed the molecular epidemiology of Typhoid Fever in Pakistan. Resistance to antimicrobial agents *S. Typhi*, he said, has become an increasing prob-

**Presentation of typhoid fever in young patients would be different from school children as they will be more atypical- Dr. Bhutta**

lem in many developing countries resulting in increased mortality and morbidity. Regular epidemic of typhoid fever has occurred in Pakistan besides being reported from India and other neighboring countries of Southeast Asia and Middle East. This study included twenty five isolates of *S. Typhi* obtained from cases of typhoid fever during 1990-91 in Rawalpindi, 122 isolates from Quetta obtained during 1993-95, thirty *S. Typhi* from Bangladesh, Six from Malaysia, eight from Kuwait and two from India which were examined. All these isolates were found to be resistant to chloramphenicol, ampicillin, tetracycline, streptomycin, sulphamethaxazole and Trimethoprim. As such they were labeled as multi-drug resistant (MDR) strains. They were however found to be sensitive to nalixidic acid, ofloxacin, ciprofloxacin, cefuroxime and cefotaxime. A single large plasmid was identified in all the MDR *S. Typhi* strains from Pakistan and every other

geographic location signifying that plasmid profiles had a limited potential for typing the isolates. This plasmid was self-transferable and encoded resistance to chloramphenicol, ampicillin, tetracycline, streptomycin, sulphamethaxazole and Trimethoprim. The Quetta Pakistan strains were found to be totally different from the rest of the isolates. Most of the Quetta isolates (97%) fall into the FIA group. The Indian, Kuwaiti, Malaysian and Bangladeshi isolates mostly fell into the HI group. However the MDR S. Typhi from Pakistan behaved differently. The Malaysian strains fell into a different and unique pattern. The Quetta Pakistan strains formed a distinct fourth pattern. All these observations point towards clonally heterogeneity MDR S. Typhi strains.

Dr. Abida Raza from Islamabad highlighted the differences in drug resistance patterns of Salmonella Typhi PCR ribotypes isolated from Pakistan. This study was conducted at NIBGE Faisalabad. Individualization of strains, she said, is important to control its spread. In recent years PCR-ribotyping that targets the 16s-

**Bone marrow culture is the gold standard for making diagnosis of typhoid fever as compared to blood culture since it is a better specimen- Prof. Ata Khan**

23s intergenic space regions has become a popular technique for discrimination of bacteria. In this study seventy-nine isolates of Salmonella Typhi were characterized by PCR-ribotyping. Sixty-one strains gave atypical pattern of three amplification products while eighteen strains exhibited a totally different pattern with only one amplification product of approximately 440bps. Twelve strains of Salmonella paratyphi-A showed homogeneity and were similar to Salmonella Typhi Type1. Resistance to chloramphenicol, Trimethoprim, amoxicillin and ciprofloxacin was 18, 16.4 and 0% respectively for Salmonella Typhi Type 1 strains while the respective results for Type II were 83.3, 72.7, 5.5 and 0%. The increased drug resistance in Type-II is interesting and it needs to be further evaluated, he remarked.

Dr. Jamil's presentation was on Enteric Fever in adult inpatients at AKUH wherein he discussed the epidemiology, clinical features and antibiotic susceptibility patterns. For this 114 case records between 1998-2000 were studied.

**Clinical presentation of Typhoid Fever includes general weakness, anorexia, headache, dizziness, abdominal pain, nausea, chills, diarrhea, muscle aches, joint pains and bowel disturbances**  
- Dr. Narain Punjabi

Age of the patient was between 15-85 years. It included 64 male and 50 female. 60% of patients were less than 26 years of age. 23.6% of patients gave a history of prior use of antibiotics Augmentin was the most commonly used drug. 97% of patients complained of fever and 51% of vomiting. Fever, bradycardia, splenomegaly and hepatomegaly were mentioned as the physical signs. Resistance to Ampicillin and Chloramphenicol was seen in 34% and 36% to Trimethoprim-sulphamethaxazole. Incidence of resistance to Ceftriaxone was (1.8%), Cefixime (0.9%) and Ofloxacin (0.9%). As expected fever was the commonest presenting complaint (84%), followed by vomiting (36%), abdominal pain (31.6%) and diarrhea (25.4%) Relative bradycardia was noted in 24% of patients; liver and spleen were palpable in 7% and 8% of patients respectively. Low platelet count was noticed in 35% of patients. For management the most common antibiotics prescribed were fluoroquinolones (70%) followed by Amoxicillin (7%) and Ceftriaxone in 3.5%. As regards the side effects, one patient had aplastic anemia that died while one patient developed seizures. This study showed that there were no localized pickets of Typhoid fever in Karachi. Fever, vomiting and abdominal pain is the most common presenting complaints and the serology tests were not found to be useful.

The next paper was from S. Bashir and colleagues from NIBGE Faisalabad titled incidence of typhoid markers in cases of Hepatitis-C. This, it was stated, is a very fatal disease and the only

proven way of transmission is through blood. In recent years some reports have emerged indicating possible relationship with pollution with sewage workers at especially high risk. But it is impossible to prove this relationship directly. It was thought that typhoid being a proven pollution related disease; determination of incidence of its markers in Hepatitis C patients would be interesting. The parameters included were PCR for typhoid and Widal test. The study included three groups i.e. PCR positive patients of Hepatitis-C (212) clinically suggestive cases of typhoid (25) and healthy controls (92). The typhoid PCR was positive in 13.6, 48 and 0% respectively. The figures for Widal test were 56.6, 68 and 34% respectively. These results they claimed show that incidence of typhoid markers in cases of Hepatitis C is higher as compared with normal population suggesting that the source of infection for the disease may be the same. Hence it does provide an indication of a relationship between pollution and Hepatitis-C.

During the discussion it was suggested that more work was needed to prove that Hepatitis-C increases the susceptibility of typhoid fever. Some of these patients it was felt might have been infected with blood earlier. Responding to a question it was stated that the AKU study in-

**The ideal diagnostic test should be sensitive, specific, quick, easy to do at bedside and free of risk but such a test is not yet available - Lt. Gen. Karamat**

cluded non-responding febrile patients who were also unable to take oral antibiotics. Dr. Mohsin Ahmad felt that blood culture should be asked even if the patient has taken some antibiotics in case of suspected cases of typhoid. Participating in the discussion Prof. Z. A. Bhutta opined that presentation in young patients could be different from school children as they are more likely to be atypical. It can be toxic illness in young children. Correlation of micronutrient malnutrition and anemia with Typhoid fever also came under discussion. Prof. Ata Khan said that blood culture is positive only in

60% of cases. The volume of blood, at which stage of the disease the patient was treated with antibiotics all matters. Hence bone marrow culture is the gold standard of making diagnosis of typhoid fever as compared to blood culture since it is a better specimen. Referring to the paper from NIBGE regarding Typhoid markers in cases of Hepatitis-C, Prof. Essa Abdullah said that pollution was not the primary cause of HCC.

### PLENARY SESSION-C

Dr. Nicholas Thomson from Sanger Center UK discussed sequencing the Genome of MDR S. Typhi CT18 while Dr. Tikki Pang from WHO

**Fluoroquinolones are the best treatment for drug resistant typhoid fever. However safety concerns besides high cost of treatment are some of the problems - Dr. Chris Parry**

spoke on Molecular Typing- an epidemiology of Typhoid Fever. He was of the view that the application of technological advances in molecular biology to the genomic analysis of S. Typhi has provided important insights into the molecular epidemiology of this pathogen. He discussed at length the application of molecular biology to the study of infectious disease epidemiology, molecular typing methods, criteria for selecting molecular typing and study of MDR ST strains. The recent sequencing of the entire genome of S. Typhi, he said, promised even greater precision and power to the application of the above approaches to studying the biology of this organism with important practical applications in disease surveillance and control. In the future perspectives he emphasized effective utilization of Genomes and study of host genetic susceptibility to infection.

Dr. Dianne Lightfoot from Australia spoke about Molecular Typing of Non-Typhoid Salmonellae, Genotypic methods and its disadvantages in detail. He also talked about plasmid DNA analysis and their potential, PulseNet-early warning system problems for food borne

diseases and Enter-net the international network for human G. I. Infection. European Commission funds the later. Australia, Japan, Canada, South Africa, EEC members sponsor regular workshops. Phenotypic methods, she concluded are still quite useful.

Dr. Shamala Devi from Malaysia had her presentation on molecular typing of MDR S. Typhi. During early 90s, she said, we had lot of cases but now the number of cases has decreased. During 1998, they had four hundred fifty cases but in the Year 2000, only two hundred cases were reported. It is because of improved sanitation, better awareness, education and hygiene. It could also be due to under reporting. During the Year 2000 resistance to all first line antibiotics was 40-60%. There is emergence of multidrug resistance. This disease is still prevalent in India, Bangladesh and Pakistan and it needs to be controlled. There is a need to identify the source of infection of outbreaks and criteria for evaluating the typing systems.

Participating in the discussion Prof. Z. A. Bhutta said that Typhoid has never been a priority with the WHO like other diseases i.e. food born diseases, HIV/AIDs etc. We lack a champion in the region. He suggested that let the EMRO region take it up otherwise no one will be pushing up the typhoid work.

#### PLENARY SESSION-D

Prof. Ata Khan along with Prof. A. G. Billoo chaired this session. Dr. Narain Punjabi from Indonesia was the first speaker whose presentation was on Clinical aspects of Typhoid Fever. Clinical presentation of typhoid fever, he said, varies. It is a flue like situation and at times it is very severe and fatal. It has an incubation period of 7-14 days and in some cases 3-60 days. The common symptoms include general weakness, anorexia, headache, dizziness, abdominal pain, nausea, chills, diarrhea etc. Typically patients experience prolonged fever and chills during high fever. He also depicted the slides of treated and untreated fever. Other symptoms include muscle aches, joint pains and bowel disturbances. Liver is always involved and it may

lead to chronic carrier state. In severe cases, linear rupture of spleen has been reported. Rose spots are also frequently reported but one has to actively look for these spots. Coated tongue is also called as furred tongue which is yet another symptom. As regards respiratory systems, lack of fluid intake leads to sore throat, cough, chest discomfort, pharyngitis and laryngitis. It can result in spontaneous abortion, premature labor and loss of hair. He then discussed the

**Right choice of antibiotics immediately at admission is very important otherwise case fatality rate will increase - Prof. Bhutta**

clinical setting in an ambulatory clinic and hospital, pediatric vs. adult patient. Host factors, he said, include reduced gastric acidity, reduced bowel motility, immune system and malfunction. Broad-spectrum antibiotics reduce the bowel flora. Sanitation and hygiene are extremely important. Male have higher chance of exposure, hence they will have more incidence. Studies from South Africa and Bangladesh have shown that female have higher rate of complications and death. Complications and relapse rate is between 5-20%. It includes intestinal perforation, bleeding, apathy and mental status alterations. He concluded his presentation by saying that history of exposure and travel to endemic area is important.

Dr. Myron Levine from Maryland USA discussed newer vaccine developments in Typhoid. Both parenteral Vi polysaccharide and oral vaccines Ty21a enteric coated capsules and Sacche are available in different countries. A single dose of Vi confers moderate protection. Ty21a is a safe, well-tolerated, effective practical oral vaccine. Over five hundred thousand kids between the ages of 5-19 years are involved in six field trials. Oral vaccines, he said, is practical in school based kids. It is important to create a favorable balance between the immunogenicity and reactogenicity. CVD 909 study is currently in progress. Concluding his presentation he said that typhoid is still a major public health problem. One parenteral vaccine is preferable in

most developing countries. Vaccine may be oral, nasal, one or two doses but it must be heat stable. Now we have safe and effective vaccines available which can be included in EPI, school based immunization programme but it is the economics and lack of political commitment to face typhoid fever as a problem in most of the developing countries.

Lt. Gen. Karamat from Pakistan spoke on changing trends in drug resistance for typhoid fever. He pointed out that about fifteen million people in developing countries suffer from typhoid fever each year. The prevalence in Pakistan is estimated to be 700/100,000 whereas in India it is 900/100,000 with antibiotics, this disease went away but now it has come back again because of drug resistance.

Typhoid, he said, is a high burden disease. Diagnosis is difficult. Inappropriate treatment with antibiotic leads to multidrug resistance. Poor preventive measures have made the situation still worse. He feared that with the increas-

**Widal is still the most popular test in various countries because it is very simple and inexpensive although it is not very specific and sensitive**  
- Dr. Pak Leong Lim

ing popularity of fast food like McDonald and KFCs the problem of typhoid will increase further in the days to come. Except big cities, qualified microbiologists and good laboratories are not available in Pakistan. Diagnosis can be made with blood culture, from clot and from bone marrow. We still continue to use Widal test because it is the cheapest although it has been discarded in many countries of the world. Typhidot test is expensive. Carrier detection rate is very poor. The carriers are roaming passing on this infection to others. Till 1987, Co-trimoxazole, ampicillin and chloramphenicol were used to treat typhoid and they were very effective. Now *S. Typhi* is decreasing whereas *S. Paratyphi-A* is on the increase. Studies done in 1995 showed that resistance to chloramphenicol, Co-trimoxazole and Ampicillin was as high as 75%, From 1996 onward resistance

started decreasing when it was between 25-28% to all these three primary antibiotics. In 2001 resistance to chloramphenicol was 31.45%, Co-trimoxazole 34.43% and to Ampicillin it was 31.15%. The ideal diagnostic test Gen. Karamat opined should be sensitive, specific, and easy to do at bedside, free of risk, quick but such a test is not yet available. We need more emphasis on prevention. Resistance to antibiotics is increasing. Control measures are well known. If we are not careful, resistance to quinolones and third generation cephalosporins will also develop. Tuberculosis is yet another big problem. WHO and the developed world must look at the problems of TB and Typhoid fever otherwise in the coming days they might themselves face these diseases. We can overcome typhoid and let the World overcome tuberculosis, he added.

Replying to a question Gen. Karamat said that there was no information on carrier state of Typhoid Fever in Pakistan because it has not yet attracted the attention of public health officials. We do come across carriers who are treated but the incidence is not more than 5%. In the Army we do follow these carriers but on the civil side it is extremely difficult, he remarked.

#### PLENARY SESSION-E

This session on the second day was chaired by Dr. Bernard Ivanoff and Dr. Naseem Salahuddin. Dr. Chris Parry from University of Oxford UK was the first speaker who talked about treatment strategies in Typhoid Fever. Speaking about the control of typhoid fever in endemic areas he opined that case finding and treatment is also a method of control of typhoid Fever if vaccines are not available. Many patients in the community are never admitted to hospital. In a study carried out in New Delhi only 10% of patients were admitted while in the Vietnam study 34% of typhoid fever patients were admitted. He discussed in detail as to who needs treatment, what is the evidence for treatment, and what is the future.

In endemic areas about 40-80% patients are children. Travelers, returning immigrants and



laboratory staff, he felt must be treated. Treatment should be effective ensuring clinical microbiological cure. It should prevent complications, mortality and resolve symptoms within seven to ten days. Giving details of various trials of chloramphenicol (21), TMP/SMX (1) and Amoxicillin (2) the relapse rate in these studies, he said, was 5.5%, 1.9% and 1.2% respectively. Third generation cephalosporins Fluoroquinolones had sixteen trials involving 984 patients. Fever was controlled in 3.7 days and relapse was only 1.3%. Three hundred sixty eight patients were enrolled in twelve trials of

**Widal has no diagnostic value. PCR is a good tool for diagnosis of typhoid fever. It takes about nine hours and at NIBGE cost Rs.700/- Dr. Haque**

Ceftriaxone. It controlled fever in 6.9 days. Fluoroquinolones, he opined, are the best treatment for drug resistant typhoid fever but it has some problems like safety and cost of treatment is also very high. It is feared that cartilage damage may be seen in some children. Reduced susceptibility and resistance are the main problems associated with fluoroquinolones. He also referred to the unpublished data wherein ofloxacin 20mg/kg was used in two doses for seven days and Azithromycin 10mg was used for seven days and there was no relapse. Azithromycin, he felt was the best for seven days treatment. In special situations like dexamethasone encephalopathy broad-spectrum antibiotics are used for management of perforation. In future we may see better use of the existing antibiotics, combination therapy for better treatment and decreased resistance while new antibiotics should also be considered. There have been sporadic reports of full fluoroquinolones and cephalosporins resistance in South Asia. More recently multidrug resistance typhoid fever has been a problem in Kenya. More clinical trials with fluoroquinolones in typhoid fever are needed. Replying to a question during the discussion regarding safety of fluoroquinolones in

children below five years of age, Dr. Chris Parry said we did not see any problem.

## **TYPHOID FEVER IN CHILDREN - THE UNANSWERED QUESTIONS**

Prof. Zulfiqar A. Bhutta was the next speaker who talked about clinical and therapeutic aspects of typhoid fever in children. Most of the studies done in Pakistan, he said, are in institutions in urban centers. According to a recent DHS survey Low Birth Weight, cardiovascular diseases, diarrhea and typhoid fever are the major causes of death in Pakistan. Typhoid fever cases have a seasonal variation and more cases are seen in August, September and October or in rainy seasons. As per lab data, almost 70% of typhoid fever cases are in children. Paratyphoid is more in adults. Almost 30-40% of admissions in hospitals due to typhoid fever were in children under five years of age. AKU data from 1995-99 shows that prevalence of multidrug resistance typhoid fever in children has now reduced to 21% as compared to 80-90% in mid 90s. Giving details of the AKU study Prof. Bhutta said that a total of 2547 patients were enrolled. It included 1504 male.1229 children

**Ultrasound can be used to diagnose typhoid fever, as a follow up modality to ascertain the extent of organ involvement, response to treatment and pick up complications like perforation early  
- Dr. Tariq Mahmood**

were less than five years of age. Only 1650 children could be followed up. The relapse rate was just 4.2% and mortality was 1.1%. Mortality in multidrug resistant typhoid fever has remained high. Almost 25% of infants with typhoid fever are afebrile and suffer from diarrhea. Multi drug resistant cases with diarrhea need more hospitalization. Since fluoroquinolones were not available in the hospital, multidrug resistant cases were treated with parenteral and oral cephalosporins. Some patients did better than others. Prof. Bhutta pointed out that the com-

munity used oral Cefixime massively when we were using it for multidrug resistant cases only. Relapse rate was below 5% and mortality rate was. Right choice of antibiotics immediately at admission is very important otherwise case fatality rate will increase. Prof. Bhutta was of the view that one must have some clinical data to make the decision regarding choice of antibiotics. As per IMS figures the use of quinolones and monobactams was greatly increasing in Karachi. A study done in Hijrat Colony and Sultanabad areas of Karachi showed that of all febrile illnesses, 17% were of typhoid fever while malaria accounted for less than 3% of the cases. Speaking about algorithm for recognition and rationale management of typhoid fever he said that a study of 219 cases showed that first line agents gave a cure rate of 97%. We might see very severe disease in young infants with more complications but the prevalence of multidrug resistance is going down. We need community-based studies and there is a need to check the overuse of second and third generation cephalosporins, he remarked.

Dr. Albert Vollard discussed risk factors for typhoid fever in Indonesia. It was a case control study. The risk factors, which he mentioned, included poor hand washing practices, eating outdoors, unhygienic water supply and open sewerage. Seventy-three patients enrolled in this study and positivity rate was found to be 21.9%. The conclusions from this study were that poor living conditions, high case of flooding, poor water supply results in higher hospitalization and high rate of contamination.

Dr. Rumina Hassan from AKU discussed quinolones susceptibility of salmonella in Enteric Fever in Karachi. In this study almost 50% of the cases were of multidrug resistance and resistance to fluoroquinolones was between 15-20%. Resistance to fluoroquinolones, she stated was now increasing.

### RECENT ADVANCES IN MICROBIOLOGY

Dr. John Wain was the first speaker in this session who spoke about recent advances in

Typhoid Microbiology. He pointed out that in Africa it is extremely difficult to take huge volume of blood for proper diagnosis. Dr. Pak Leong Lim from Hong Kong talked about the serological diagnostic aspects of typhoid. He discussed in detail the isolation of organism, detection by PCR, serology antigen and antibody detection. Widal, he stated, is still the most popular test in various countries because it is very simple and inexpensive although it is not very specific and sensitive. However positive Widal gives some idea of some infection. Typhidot, he said has a sensitivity of 95% and specificity of over 85%. During the discussion it was pointed out that although the new test is more reliable but Widal is user friendly and affordable. Tubex test is one step based, one color positive and negative. Tubex has a sensitivity of 87% and specificity of 76%, which was not so good. LPs dipstick has a sensitivity of 77% and specificity of 95%.

Dr. Abdul Haque from NIBGE Faisalabad discussed PCR based diagnosis for typhoid fever- the Pakistani experience. The currently available diagnostic procedures, he said, include the

**In the absence of blood, bone marrow culture, Typhidot has become the diagnostic standard for enteric fever at FGS hospital - Dr. Imtiaz Hassan**

Widal test, bone marrow and cord blood culture. Typhoid, he said is quite common and we need a reliable diagnostic method which is also affordable. Widal is the most commonly used test to make diagnosis for typhoid fever. Typhidot is Elisa based test, which is more sensitive and specific than Widal test. As regards PCR based method of test, four different approaches are reported. Our experience showed that PCR is 93% sensitive and has 100% specificity. PCR (Vi gene) can detect even a single cell. It was reported but later on discarded since Vi antigen is not present in all strains. At NIBGE Dr. Haque said, we made certain modifications for PCR targeting flick gene in terms of ease of processing of samples and sensitivity. Before introducing this technique for public benefit, three different studies involving patient of early

typhoid and problematic cases of typhoid were carried out and the comparisons were made with blood culture, Widal test and Typhidot. These studies involved 227 individuals and it showed that PCR based diagnostic procedures used by us at NIBGE was much better in sensitivity in comparison with other methods. The specificity was almost as good as blood culture. It compared favorably with Typhidot and was much superior to Widal test. In 162 cases of suspected typhoid, PCR blood culture and Widal test was positive in 66.6, 23.4 and 45.1% cases respectively. The respective figures for 65 controls were 1.5%, 0% and 30.8%. Typhidot was more specific than Widal test. His conclusions were that Widal has no diagnostic value. PCR is a good tool for diagnosis of typhoid fever. Responding to a question during the discussion Dr. Haque said that it takes about nine hours and we charge seven hundred rupees for this test.

Speaking on role of Widal test in diagnosis of typhoid fever Dr. Khalid Imam said that Widal test ordered during the first few days of typhoid

**We have done 12,000 tests with Typhidot. When physicians ask, we do the blood culture as well. We usually get the result on first or second day of fever**  
- Prof. Essa Abdullah

fever could be negative since enough antibodies may not have developed by then. His presentation was based on a study of 258 samples of patients between 12-86 years of age. 46 were culture proven cases, 33 were positive with Widal and 13 negative on Widal test. Fifty-nine healthy patients were in the control group in which Widal was positive in many cases. In view of the high false positive and high false negative Widal test is not recommended. Blood tissue culture, he opined was the most effective method for making diagnosis of typhoid fever.

Dr. Tariq Mahmood from JPMC discussed the role of ultrasound in diagnosis of typhoid fever. He conducted this study at JPMC, 7th Day Adventist Hospital and PNS Shifa. Four hun-

dred fifty patients were included in the study. The age of patients was between 2-56 years. Most of the patients presented with fever, diarrhea and headache after four to seven. In 367 patients there were some multiple findings, which can be seen only in typhoid fever and no other disease. As such, ultrasound, he stated has a definite role for rapid and effective diagnosis of typhoid fever. This is an efficient modality, which can be used not only to diagnose typhoid fever but also as a follow up modality to ascertain the extent of organ involvement, response to treatment, pick up complications like perforation early in the pre clinical phase.

Participating in the discussion Prof. Z.A. Bhutta said that this data offers an opportunity for collaboration between pediatricians and radiologists for diagnosis of typhoid fever particularly in children. Responding to a question Dr. Tariq Mahmood said that it takes about twenty minutes to examine the abdomen thoroughly by ultrasound.

Dr. Ashraf Memon's presentation was on need to improve quality control in Labs to standardize Typhidot procedure for correct and authentic reporting. His presentation was based on a visit to thirty laboratories to observe the testing procedures. Laboratory staff was also interviewed. Various deficiencies like dilution error, use of cold kits, contamination, poor pipetting techniques, use of poor quality of deionised water, improper storage of reagents, improper technique of reading color of dots etc., were noted. Remedial measures were discussed with the lab staff after which the Typhidot results improved significantly, he added.

Dr. Imtiaz Hasan from Islamabad spoke on criterion for Typhidot EIA testing and its use as standard for diagnosis of enteric fever. Federal Government Services Hospital in Islamabad he stated was one of the first hospitals to start using Typhidot test. Forty three children between the age of eleven months to one year were enrolled in this study conducted between 1999-2000. Most of the children had some sort of antibiotic making blood culture meaningless. Bone marrow was not available. Some patients, adults and children with long standing pyrexia of un-

known origin negative to Widal reaction were also tested. Our results, he said, show a consistent pattern in which patients with pyrexia of 5-10 days duration, tested positive on Typhidot while negative on Widal reaction. These same patients tested during the third week of fever commonly became Widal positive. On the basis of these findings we have established our selection criteria for Typhidot tests. It includes patients with fever of ten days or less and secondly patients of long standing PUO negative to Widal reaction. These criteria, Dr. Imtiaz Hassan stated have served well to conserve material and manpower resources. Typhidot is relatively expensive and labor intensive but it ensures early and reliable diagnosis to the clinicians. In the absence of blood culture, bone marrow culture, Typhidot he said has become the diagnostic standard for enteric fever at our hospital.

During the discussion it was stated that almost 50% of teaching institutions do not have facilities for reliable serological test. There is an urgent need to have good reliable serological

tests. Prof. Essa Abdullah said that we started using Typhidot test to diagnose typhoid fever when no one else was using it. So far we have done twelve thousand cases. When the physicians ask, we do the blood culture as well. We usually get the result on first or second day of fever, he added. Prof. Shahana Urooj Kazmi highlighted the findings of their study regarding a new antimicrobial preparation for multidrug resistant salmonellae named as Amoxycassia. She presented the animal study results as well. This preparation she stated has been patented and more studies are planned. Dr. Irshad Sethi from Karachi discussed diagnosis of atypical presentations of typhoid fever. An important highlight of the symposium was that everything went on as scheduled. The inaugural session as well as the scientific sessions started in time, most of the speakers kept to the allotted time leaving enough time for the discussion. Dr. Robert F. Maudsley Dean Faculty of Health Sciences was the chief guest at the dinner hosted in honor of the delegates and participants on February 6th.