20 YEARS OF PROGRESS IN DIARRHEAL DISEASE RESEARCH

Narain H. Punjabi¹, Nancy D. Witham¹, Donald H. Burr¹,
Cyrus H. Simanjuntak², Murad Lesmana¹, S. Suharyono³, Sunoto³,
Maramis A. Hisham⁴, Atti R. Rivai⁴, Swiandy Kumala⁴,
Y. Soenarto⁵, and S. Komalarini⁶

When NAMRU started its collaboration work with the National Institute of Health, Research and Development (NIHRD), it became apparent that diarrheal disease was one of the most important causes of morbidity and mortality in Indonesia, especially in children¹. Many of the most important etiologic agents of diarrhea were not known and the percentage of diarrheas with an identifiable etiologic agent was very low².

Since these early times NAMRU and NIHRD have worked together in all aspects of diarrheal disease research. Increased capabilities for the identification of bacteriologic, parasitic and viral enteropathogens, new vaccines, and better treatment via oral rehydration solutions are some of the results of this collaboration.

ETIOLOGY

The majority of the earlier work done by NAMRU and NIHRD was in the area of etiologies of diarrhea and gastrointestinal disease, focusing on cholera and other *Vibrio* species, and intestinal parasitism. In 1971, Joseph and co-workers were the first to report in Indonesia the unsuspected association of *Vibrio parahaemolyticus* with diarrheal disease³-⁵. The clinical picture of the patients with *V. parahaemolyticus* infection was not significantly different from those with other commonly identified etiologies. Later in 1977, Komalarini et al. reported on a 21 month study of the etiology of diarrhea among infants and children admitted to Sumber Waras Hospital⁶. The major etiologic pathogen detected was *Vibrio cholerae* biotype El tor. Other important etiologies of diarrhea observed in this study were *Salmonella*, *Shigella*, *Vibrio cholerae* non-01, and *V. parahaemolyticus*. A bimodal seasonal pattern of admitted cases occurred, with peaks during or immediately after the dry and rainy seasons. However, in later studies it was shown that these annual patterns of seasonality and morbidity were subject to significant long-term fluctuations⁶,¹⁰-¹¹,¹³.

The first isolation in Indonesia of *Campylobacter jejuni* from Indonesian patients

¹ U.S. Naval Medical Research Unit No. 2, Jakarta
² National Institute of Health Research and Development, Jakarta
³ Department of Child Health, Faculty of Medicine, University of Indonesia, Jakarta
⁴ Infectious Disease Hospital, Jakarta
⁵ Department of Child Health, Faculty of Medicine, Gadjah Mada University, Yogyakarta
⁶ Department of Child Health, Sumber Waras Hospital, Jakarta
with gastroenteritis was made by Ringertz et al in 1980. In this study, Campylobacter was isolated from feces of 15 of 144 diarrheic children less than 9 years of age, and from 4 of 251 adults with gastroenteritis. In contrast, Campylobacter spp. was isolated from only 1 child in a control group of 221 persons. Subsequent work, determined the susceptibility of this organism to a wide range of antimicrobial agents.

Several other diarrhea studies were done in the following years with different objectives. A study done in Yogyakarta in 1975 aimed to determine the relation between bacteria isolated from stool culture and presence of leucocytes in feces. Sunoto et al. in 1978 reported the effects of commonly utilized antibiotics on 2 groups of children infected with entero-pathogenic bacteria who were treated with oral rehydration solution (ORS). The result showed no significant difference between the group of children who received ORS plus antibiotic and the group who was given ORS only. In 1980 Punjabi et al. compared the results of stool/rectal swab cultures from adult diarrheal patients to febrile patients hospitalized at Infectious Disease Hospital of Jakarta. Agents of diarrhea, including rotavirus and enterotoxigenic E. coli (ETEC), were detected in 84% of diarrhea patients. From the group of febrile patients positive isolation was observed in 44%, however, 39% were Salmonella spp., (27% S. typhi, 7% S. paratyphi and 5% Salmonella C1) which were leading cause febrile patients admission into this hospital. In 1982 Gracey et al. reported a 10% frequency of isolation for Aeromonas spp. among children who were hospitalized in Jakarta for diarrhea. Aeromonas spp., in much lower percentage, was also reported by Rockhill et al. in 1982 during a 16 month period of observation looking into enteropathogens from diarrhea patients. In 1986, Komalarini et al. reported the detection of rotavirus in stools from 31% of diarrhea children less than five years of age during a one year study. Other enteropathogens detected were: Salmonella (10%), V. cholerae (7%), Shigella spp. (0.8%) and Campylobacter spp. (0.3%).

Progress continued to be made toward better identification of pathogens responsible for diarrhea when Burr et al., during 1988-1990 looked into the etiology of diarrhea among expatriates living in Jakarta. In this study, the list of identifiable pathogens was expanded to include new types of pathogenic E. coli: EHEC (entero hemorrhagic E. coli), EAEC (entero adherens E. coli), EIEC (entero invasive E. coli), Yersinia enterocolica, adenovirus and Cryptosporidium spp.

In addition to the identification of enteropathogen in human materials, NAMRU and collaborators also investigate environmental and food contamination by diarrheal pathogens. Results from testing water samples collected during 1973-74 from the Ciliwung River, Jakarta's main river, Tjaniadi and Hadiputranto et al. in 1974 showed the presence of large numbers of coliform bacteria, including Salmonella spp. and S. typhi. Similar levels of contamination reported by Gracey et al. in 1976, indicated fecal pollution of Jakarta's rivers was a significant public health problem. While investigating food and ice sold in Jakarta's streets, Hadiputranto and Rockhill in 1982 reported that 38% of samples had total and fecal
coliform contamination, while others had lesser but significant contamination with *Ps. aeroginosa*, *S. epidermis*, and *B. cereus*. However, there were no isolates of common bacterial enteropathogens such as *Salmonella* spp., *Shigella* spp., *V. cholerae*, *Aeromonas* or *C. botulinum*.

**RAPID DIAGNOSIS**

The development of rapid methods for the detection of enteropathogens has concentrated primarily on the rapid diagnosis of *V. cholerae*. Lesmana and Rockhill *et al.* in 1982 reported on a coagglutination test for the rapid identification of *V. cholerae* using heat treated, stabilized protein A containing staphylococci to which anti-cholera antiserum is attached. This highly sensitive and specific method was able to detect *V. cholerae* antigen in enrichment cultures from feces after only 8 hours of incubation. Lesmana *et al.* also showed that the coagglutination test could be used as a preliminary screen to detect *V. cholerae* on primary isolation plates, even when overgrown with other bacteria.

**TREATMENT**

A collaborative effort between NAMRU, NIHRD and Infectious Diseases Hospital of Jakarta to study treatment of infectious diarrhea has focused principally on continued evaluation of the WHO program for oral rehydration solutions. In a randomized, double-blind controlled trial of almost 200 secretory diarrhea cases including cholera patients, it was shown that a citrate-based ORS was superior compared to bicarbonate based ORS in reducing all the parameters clinicians consider important in assessing improvement from an episode of severe diarrhea. Use of the citrate-based ORS was associated with a reduced incidence of vomiting, decreased stool output, and faster clinical normalization. This result and other results from similar studies performed in different centers, led to the world-wide recommendation by WHO for use of the citrated ORS preparation instead of bicarbonate base.

A glycine supplemented ORS formula was evaluated in Jakarta during 1987 and was shown to be no more effective than the standard citrated ORS. More recently, a similar trial compared the standard citrated with glucose based ORS to a powdered, pre-cooked, rice based ORS. In addition to improved palatability, the rice ORS was associated with greater reductions in stool output.

**PREVENTION**

Until recently, NIHRD and NAMRU had not been actively involved in research for the prevention of diarrhea. In 1989, the Center for Vaccine Development in Baltimore, Maryland, USA solicited our involvement in a safety and immunogenicity trial of a recombinant DNA oral cholera vaccine in Indonesia. Preliminary results have shown a well-tolerated vaccine that with lower dose has a poorer immunogenicity in Indonesian compared to North American volunteers. Utilizing higher dose, the immunogenicity was much improved without significant increase in side effect.
REFERENCES


20 years of progress in diarrheal . . . . . . . Narain H. Punjabi et al.


