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SPECIAL ARTICLE

Personal Reflections on the Discovery of *Vibrio cholerae* 0139 Synonym Bengal: A Tribute to Team Work and International Collaboration

The emergence of *Vibrio cholerae* 0139 synonym Bengal in the late part of 1992 is a unique event in the history of cholera. It shattered the long - held notion that the 01 serogroup of *V. cholerae* is the only serogroup that is capable of causing epidemics and pandemics of cholera.

The story of the emergence of *V. cholerae* 0139 Bengal is not only interesting from a medical point of view, but also as a story of general scientific discovery. It illustrates the value of communication and collaboration between scientific groups in achieving rapid breakthroughs which may ultimately benefit all mankind. In this communication, I will try to recount events that unfolded in the discovery of *V. cholerae* 0139 Bengal as they became known to me by my personal involvement in the work, personal interaction with various scientists, and published reports.

V. cholerae 0139 first caught the attention of the world when it caused large outbreaks of clinical cholera in the south Indian port city of Madras in October 1992. Soon afterwards, the occurrence of outbreaks were noted in other southern Indian cities of Vellore and Madurai. The outbreak isolates were sent to the National Institute of Cholera and Enteric Diseases (NICED) in Calcutta (north - eastern India) for identification. Dr. G. Balakrish Nair, a microbiologist at NICED, could not type the isolates with antisera to *V. cholerae* 01, a naturally suspected pathogen for such outbreaks of clinical cholera. Therefore, by conventional definition, the outbreak strain was called a *V. cholerae* non - 01. Starting in November 1992, an unusual increase in the rate of isolation of *V. cholerae* non - 01 was noted among the patients with cholera admitted to the Infectious Diseases Hospital (IDH) in Calcutta. By the end of December 1992, *V. cholerae* non - 01 isolates predominated in cholera patients seen at the IDH. Dr. G.B. Nair sent a collection of epidemic *V. cholerae* non - 01 isolates from southern India and Calcutta to Dr. T. Shimada at the National Institute of Health, Tokyo, Japan for serogrouping. Dr. Shimada is probably the only cholera microbiologist in the world who has diligently developed a laborious and extensive serogrouping scheme for *V. cholerae*. By hindsight, it appeared that history would reward him with a lucky break for his hard work.

Cholera is endemic in southern Bangladesh as in the rest of the country. In December 1992, the Government of Bangladesh reported an epidemic of diarrhoea in southern Bangladesh, and the physicians of the Epidemic Control Preparedness Programme (ECPP) of the International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) investigated the outbreak in early January 1993, and found the diarrhoeal cases to be typically cholera. Moreover, most of the victims were adults, an unusual departure from the usual pattern in cholera outbreaks where in a cholera endemic country (Bangladesh), usually children are predominantly affected. Rectal swab cultures performed on a sample of these patients yielded only *V. cholerae* non - 01. This went against the commonly held belief that *V. cholerae* non - 01 do not cause large outbreaks of diarrhoea and aroused our suspicion that we have an unusual cholera organism in the midst of a virgin population. It also suggested that previous exposure of the population to *V. cholerae* 01 in this cholera endemic country did not seem to afford any cross - protection.

Every year, in the third week of January, Bangladesh hosts the second largest Islamic religious gathering next to the gathering in Mecca. This gathering called "Bishwa Istama" is held on the banks of the Turag river about 20 km north of the capital city, Dhaka. About 2 million pilgrims from the Indian subcontinent and the surrounding areas attend the gathering. The conditions at the meeting place are very crowded and the hygienic practices very inadequate. Water from the polluted river is used for washing and drinking, offering ample opportunities for the spread of enteric infections. Several pilgrims attending the gathering in January 1993 developed clinical cholera and sought treatment at the treatment centre of ICDDR,B, located in Dhaka. But, even though we cultured *V. cholerae* non - 01 from some of these patients, we failed to recognize their importance and the isolates were not kept. The patients' addresses were also not recorded since they came from far away places. By retrospective analysis, it appears that *V. cholerae* 0139 was probably introduced into Dhaka by pilgrims either from southern Bangladesh or from India. Soon afterwards, an unusually large number of adult cholera patients began to be seen at the Dhaka

treatment centre of ICDDR,B. Rectal swab cultures from these patients also yielded mainly *V. cholerae* non−01 isolates. Field isolates from southern Bangladesh and the isolates from the hospitalized patients in Dhaka were identical, and they resembled *V. cholerae* 01 in most respects, including the ability to produce cholera toxin (a *sine quo non* for *V. cholerae* 01) except for their non−agglutinability in *V. cholerae* 01 antiserum. This led us to suspect initially that the epidemic strain could be an O antigenic mutant of *V. cholerae* 01 that has lost its agglutinability. By this time, it became apparent to us that a rare event had occurred in the history of cholera and that it was important to identify the serogroup of this epidemic strain. In the first week of February, I sought the help of Dr. Shimada to serogroup the isolates, and he gladly obliged. In the meantime, we felt that it was important to quickly publish the findings.

I met him at the Dhaka airport, I told him about the unusual outbreak of clinical cholera due to a *V. cholerae* non−01 in Bangladesh, and instantly he disclosed that similar outbreaks were also occurring in several parts of India. In the next few days of Dr. Nair's stay with us, he, Dr. Sack and I agreed that we should send separate letters simultaneously from NICED and ICDDR,B about the outbreaks to *The Lancet* for publication. We also agreed to exchange copies of each other's letters before submission. Within a few days of Dr. Nair's return to Calcutta, we received a draft of his letter by fax and we also faxed him a copy of ours. By this time, Dr. Nair had received the serogrouping report from Dr. Shimada that the epidemic isolates could not be typed with the antisera to the already known 138 serogroups of *V. cholerae* (*V. cholerae* 01 and 137 serogroups of *V. cholerae* non−01). This information could be included in Dr. Nair's letter to

The gathering at *Bishwa Istama* showing pilgrims cooking on the banks of the Turag river. *Golam Rabbani*

Earlier, Dr. R. Bradley Sack, who is the Associate Director of Laboratory Sciences and Community Health Divisions at the ICDDR,B, felt that since ICDDR,B and NICED are engaged in similar kinds of research, they should have more collaborative links. At his urging, I paid a visit to NICED in May 1992, and we invited Dr. Nair from NICED for a return visit to ICDDR,B. Perhaps, it was coincidental (but, nevertheless, now historically mutually rewarding) that he decided to visit ICDDR,B in the third week of February 1993. When

The Lancet. However, such information was not available for Bangladeshi isolates for inclusion in our letter to *The Lancet*. Both letters were published side by side in *The Lancet*'s March 13, 1993 issue (1,2). Subsequently, in the April 24, 1993 issue of *The Lancet*, Drs. M.V. Jesudason and T.J. John from the Christian Medical College Hospital, Vellore reported that, starting in April 1991, an unusually high isolation rate of *V. cholerae* non−01 was observed there. In the following year, the usually predominant *V. cholerae* 01 to *V. cholerae* non−01

isolation ratio was reversed in Vellore (3). It is not known whether the *V. cholerae* non-01 isolates of 1991 from Vellore were later confirmed as *V. cholerae* 0139.

On March 18, 1993, I received a fax from Dr. Shimada on the serogrouping results of the epidemic *V. cholerae* non-01 isolates. Like the isolates from India, the Bangladeshi isolates also could not be serogrouped with the antisera to the existing 138 serogroups of *V. cholerae*. Subsequently with an antiserum prepared to an isolate from Madras, Dr. Shimada determined that both the Indian and Bangladeshi epidemic isolates were serologically identical to each other and decided to give a new serogroup number 0139, the next consecutive number for a new serogroup. On April 21, 1993, I received a fax message from Dr. Yoshifumi Takeda, Kyoto University, Japan, with whom Dr. Nair collaborated on the characterization of epidemic isolates, that Dr. Shimada wanted to publish the new serogroup information of the epidemic isolates. He also mentioned that Dr. Shimada, Dr. Nair, and he were drafting a letter for submission to *The Lancet*, and invited me and others from ICDDR,B to join as co-authors of the letter. He suggested that the epidemic strain be called "serogroup 0139 scpal". (Dr. S.C. Pal was a former Director of NICED, who passed away a few months earlier.) However, we felt that it was not appropriate to give the synonym "scpal" to the epidemic isolates since Dr. Pal was not associated with the discovery of, and significant work on, the organism, the two most important criteria for assigning a person's name to a new organism. On the other hand, I felt that the credit for the discovery of *V. cholerae* 0139 should be shared by workers both at NICED and ICDDR,B, and I tried to coin a term to be given to the epidemic strain by combining the acronyms of both the institutes. But it was not possible to coin a phonetically-pleasing name in this way. Then I thought that the synonym "Bengal" might be appropriate because the epidemic strain was first isolated from the east coast of the Indian subcontinent on the Bay of Bengal and it encompassed both India and Bangladesh. I conveyed my thoughts to Dr. Sack and he agreed with my proposal. Then I faxed this proposal to Dr. Takeda. He and his colleagues embraced the idea and a joint letter was immediately submitted to *The Lancet*, which was published in the May 22, 1993 issue of the journal (4).

In subsequent months, cholera cases due to *V. cholerae* 0139 continued to rise in Dhaka and in the rural Matlab, where ICDDR,B maintains another treatment facility. Cholera cases due to *V. cholerae* 01 virtually disappeared in Dhaka. *V. cholerae* 0139 continued to invade new territories in the country. In the meantime, work on the new cholera continued at ICDDR,B on many fronts. Dr. Demissie Habte, the Director of ICDDR,B, felt that all scientists should work together and publish a comprehensive report of the new disease. Accordingly, laboratory scientists, physicians and epidemiologists, as a Cholera Working Group, met together on a number of occasions under the chairmanship of Dr. Sack and prepared a comprehensive report, which was submitted to *The Lancet* on May 12, 1993. This report was published as a full-length article in the August 14, 1993 issue of the prestigenous journal (5).

The saga of *V. cholerae* 0139 still continues. Now the disease has engulfed almost the entire Indian subcontinent and is poised to take on the whole world. At the present time, there are documented cases in Nepal, Thailand, Malaysia, Pakistan, China, and Saudi Arabia. There is at least one report of an imported case to the United States (6). This strain is almost certainly the "eighth pandemic" strain of cholera (7) and is spreading at breakneck speed compared to the seventh pandemic strain, which has travelled very slowly taking almost 30 years to reach the South American continent (8).

It is heartening to look back and savour how the 0139 story has unfolded in the first few months. The scientists especially in India, Bangladeşh, and Japan scrambled to quickly characterize the organism and the disease, and disseminate the findings, making the world medical community aware of the new threat and alerting it to be prepared to tackle the challenge in the event it appeared in new areas. Wide publicity was also given by the world press and audiovisual media. We have responded to innumerable requests for supplies of reference strains and diagnostic reagents from laboratories around the world. We have also teamed up with scientists in several industrialized countries for further characterization of the epidemic strain and for making suitable vaccines. Useful monoclonal antibodies have been prepared in our laboratory which are being used in the development of simple and rapid diagnostic tests. Candidate vaccines will be available for volunteer studies in early 1994.

These remarkable developments have taken place in a short span of less than a year. All these have been possible because of the team work and international collaboration across continents. Robert Koch, who had contributed so much to infectious diseases, and who was also the first to isolate *V. cholerae* 01 more than a century ago, would have been truly impressed by our achievements, if he had lived in our times. Even so, let us not be complacent lest greater challenges in the future overtake us.

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M John Albert

Research Microbiologist and Head, Department of Laboratory Research, Laboratory Sciences Division, International Centre for Diarrhoeal Disease Research, Bangladesh, GPO Box 128, Dhaka 1000, Bangladesh