Journal of
Medical Microbiology & Diagnosis

Khan and Anil Kumar, J Med Microb Diagn 2014, 3:1
DOI: 10.4172/2161-0703.1000e124

Editorial Open Access

Typhoid Diagnostics for the Developing World - Are We Looking in the Wrong Haystack?

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Typhoid fever has never been a proverbial closet disease. It has changed the course of history more than once, be it in the form of the devastating plague of Athens in 430-426 B.C that ended the Golden age of Pericles or the death of Alexander the Great [1,2]. Agreed that with access to better sanitation and healthcare, typhoid fever has dropped out of recent memory of the developed world. Nevertheless, it still affects 21 million people around the globe; killing 216,000 people annually; a majority of the world's cases being accounted for by three countries alone-India, Pakistan and Bangladesh [3,4]. It is this statistics that still keeps public health professionals worried about typhoid, making it a giant that cannot be pushed back into any closet.

Several approaches exist to the diagnosis of enteric fever-clinical features, culture techniques, serology and molecular techniques. For decades the clinical diagnosis of typhoid fever has been a medical challenge due to its protean manifestations and similarities to other febrile illnesses.

Currently, culture from a sterile site (blood, bone marrow) followed by microbial identification is considered the gold standard in typhoid diagnostics [5]. Unfortunately, typhoid is known to be an atypical bacteremia-with low numbers of bacteria in the bloodstream, bacteremia with endotoxin negative sera, chronic and benign bacteremia and disappearance of the bacteria from the bloodstream coincident with the peak of antibody response [6]. Numerous factors hold the yield of this "gold standard" test to ransom-like the culture system/media employed, volume of blood used for culture, time of blood collection, intracellular nature of the bacteria, host's immune response, prior use of antibiotics etc. Semi-automated blood culture systems have lowered the detection time of typhoid bacilli to 18-44 hours [7]. However, their sensitivity remains comparable to conventional blood cultures and they are financially out of reach of suburban, rural and non-profit laboratories in the developing world. Researchers have postulated the optimization of *S. Typhi* cultures by exploiting its atypical biochemical properties. While genomics has highlighted the down regulation of certain metabolic pathways due to accumulation of pseudogenes in Salmonellae, an understanding of processes that up regulate metabolic pathways in order to optimize culture methods for *S. Typhi* is required [8].

In endemic regions, serological tests for typhoid provide an economical and faster diagnostic option as compared to culture methods. The Widal agglutination test, a century old test is the classical and most commonly used serological method for the diagnosis of enteric fever. The test detects antibodies to *S. Typhi* O, H and Paratyphi A & B H antigens in serial dilutions of patient sera. An acute phase single tube Widal has found to correctly diagnose 74% of the blood culture positive cases of typhoid fever [9]. For better utilization of the test, a cut-off titer has to be determined in each geographic area. Efforts over the past two decades to improve the classical Widal test have resulted in development of certain commercial assays like Tubex and Typhidot. However these tests do not diagnose paratyphoid fever and with reports of emergence of paratyphoid fever in the developing world, their practical utility remains questionable [10]. Assessment of these assays in population based surveillance studies in several countries have shown sensitivity and specificity of Tubex and Typhidot to be around 70% and 80% only [4,11]. Researchers have not identified any immunodominant antigens other than the classical antigens used in these serological tests which can be used for developing rapid diagnostic tests [8]. Therefore in the current scenario, it is a very rare serological study that reports specificity and sensitivity above 95%; which implies thatat least 1 out of 20 patients is misdiagnosed-something unacceptable in the 21st century for such a widespread disease!

Molecular techniques targeting the pathogen's genome have been studied in several centers around the globe [12,13]. The *S. Typhi* flagellin gene, fliC has been targeted in numerous PCR studies conducted on blood samples [4,8,12-14]. PCR has an additional advantage of amplifying DNA of dead bacteria which can be useful in establishing a diagnosis if treatment has already been started. However, poor sensitivity in certain studies and strong evidence supporting the PCR results being related to the number of colony forming units in blood has cast serious doubts about PCR being a robust diagnostic tool from blood samples for enteric fever [8].

Mass spectrometry, microarrays and biomarkers from proteonomic studies for typhoid are still in formulatory stages.

To cut a long story short, typhoid diagnostics is still a difficult field for developing world laboratories. While culture methods cannot be replaced because of the invaluable susceptibility data that they provide, enrichment methods and employment of media that selectively enhance typhoid bacilli cannot be over emphasized. With molecular methods being out of reach of the average laboratory, it is serology that forms the backbone of typhoid fever diagnostics in developing countries. As serological tests suffer from low sensitivity and specificity as well as frequent cross-reactions, diagnosis of typhoid fever is still a challenge in these areas. It is heartening to see Foundation Merieux, a member of Coalition against Typhoid, launch a project to develop sensitive molecular diagnostic tests for typhoid and paratyphoid fever in high burden communities.

While we wait for an innovation that changes the face of typhoid diagnostics, the role of effective control and prevention policies at a national level cannot be overemphasized. Even though WHO has

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Received February 11, 2014; **Accepted** February 12, 2014; **Published** February 14, 2014

Citation: Khan S, Anil Kumar V (2014) Typhoid Diagnostics for the Developing World - Are We Looking in the Wrong Haystack? J Med Microb Diagn 3: e124. doi:10.4172/2161-0703.1000e124

recommended typhoid vaccination in endemic regions, there have been few takers [15]. In 2011, WHO approved the procurement of injectable typhoid vaccine at low cost by developing countries through the UN vaccine procurement system. However, the response from governments in typhoid endemic countries in implementation of a vaccine against typhoid has been lukewarm. The lack of data on the cost-effectiveness of the vaccine, 65-70% efficacy and short duration of protection may be some reasons for not introducing typhoid vaccines. It is imperative for policy makers to understand that while better diagnostics will give us an estimate of the disease burden, it is immunization which will actually control typhoid fever.

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